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SCORE Placeholder Sheet for IFW Content

Application Number: 15467648 Document Date: 03/23/2017

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Form Revision Date: August 26, 2013

PTO/AIA/15 (03-13)
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U.S. Patent and Trademark Office. U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	**SYPA-009/C04US**
First Inventor	**Stephen COMISKEY**
Title	**FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. ☒ **Applicant asserts small entity status.** See 37 CFR 1.27.
3. ☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. ☒ **Specification** [*Total Pages* **148**] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. ☒ **Drawing(s).** (*35 U.S.C. 113*) [*Total Sheets* **6**]
6. **Inventor's Oath or Declaration** [*Total Sheets* **8**] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. ☐ Newly executed (original or copy)
   b. ☒ A copy from a prior application (37 CFR 1.63(d))
7. ☒ **Application Data Sheet** **See Note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. ☐ **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** *(if applicable, items a. – c. are required)*
   a. ☒ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450**

ACCOMPANYING APPLICATION PARTS

10. ☐ **Assignment Papers** (cover sheet & document(s)) Name of Assignee _____
11. ☐ **37 CFR 3.73(c) Statement** ☐ **Power of Attorney** *(when there is an assignee)*
12. ☐ **English Translation Document** *(if applicable)*
13. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
14. ☐ **Preliminary Amendment**
15. ☐ **Return Receipt Postcard** *(MPEP § 503) (Should be specifically itemized)*
16. ☐ **Certified Copy of Priority Document(s)** *(if foreign priority is claimed)*
17. ☐ **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. ☐ **Other:**

***Note**: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

☒ The address associated with Customer Number: **58249** **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Anne E. Fleckenstein/	Date	March 23, 2017
Name (Print/Type)	Anne E. Fleckenstein	Registration No. (Attorney/Agent)	62,951

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Filer:	Anne Elizabeth Fleckenstein
Attorney Docket Number:	SYPA-009C04US 321994-

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	70	70
UTILITY SEARCH FEE	2111	1	300	300
UTILITY EXAMINATION FEE	2311	1	360	360
Pages:				
UTILITY APPL SIZE FEE PER 50 SHEETS >100	2081	1	200	200
Claims:				
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**930**

Electronic Acknowledgement Receipt

EFS ID:	28715614
Application Number:	15467648
International Application Number:	
Confirmation Number:	2133
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009C04US 321994-
Receipt Date:	23-MAR-2017
Filing Date:	
Time Stamp:	16:29:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$930
RAM confirmation Number	032417INTEFSW00016915501283
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	SYPA_009_C04US_ADS.pdf	1793952 7e8e69fa21de76bc43fdcabfcf0847806774028c	no	10
Warnings:					
Information:					
2		SYPA_009_C04US_Application.pdf	818629 7a318e564c5a1e9b53035dc48ab32263c779eb8c	yes	148

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	145
Claims	146	147
Abstract	148	148

Warnings:					
Information:					
3	Drawings-only black and white line drawings	SYPA_009_C04US_Drawings.pdf	478132 f49c0e28d03942783023adbafa98ff46666e2607	no	6
Warnings:					
Information:					
4	Oath or Declaration filed	SYPA_009_C04US_Declaration.pdf	931375 926b57d2ab04c16243e8f3b89a92c40520e2c48f	no	8
Warnings:					
Information:					
5	Transmittal of New Application	SYPA_009_C04US_Transmittal.pdf	230955 a4ed90c32fd1b7881b7f0a9335e3725689264572	no	1

Warnings:					
Information:					
6	Sequence Listing (Text File)	SYPA_009_C04US_SeqList_St25.txt	115883 	no	-
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	36884 d57bad77c534e7cd2c24e9209c60ec393c56d937	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	4405810	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C04US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Stephen		COMISKEY	

Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
Doylestown	PA	US

Mailing Address of Inventor:

Address 1	105 Steeplechase Drive
Address 2	
City	Doylestown
State/Province	PA
Postal Code	18902
Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Rong		FENG	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
Langhorne	PA	US

Mailing Address of Inventor:

Address 1	74 Pine Glen Road
Address 2	
City	Langhorne
State/Province	PA
Postal Code	19047
Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	John		FOSS	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C04US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

City	Doylestown	State/Province	PA	Country of Residence	US

Mailing Address of Inventor:

Address 1	625 Linden Avenue		
Address 2			
City	Doylestown	State/Province	PA
Postal Code	18901	Country	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Kunwar		SHAILUBHAI	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Audubon	State/Province	PA	Country of Residence	US

Mailing Address of Inventor:

Address 1	2707 Bald Eagle Circle		
Address 2			
City	Audubon	State/Province	PA
Postal Code	19403	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	58249		
Email Address	ZPATDCDOCKETING@COOLEY.COM	Add Email	Remove Email

Application Information:

Title of the Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE		
Attorney Docket Number	SYPA-009/C04US	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	6	Suggested Figure for Publication (if any)	

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C04US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	58249		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	14845644	2015-09-04

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C04US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14845644	Continuation of	14661299	2015-03-18
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14661299	Continuation of	13421769	2012-03-15
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13421769	Continuation in part of	PCTUS2011051805	2011-09-15
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS2011051805	Claims benefit of provisional	61392186	2010-10-12
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS2011051805	Claims benefit of provisional	61387636	2010-09-29
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS2011051805	Claims benefit of provisional	61383156	2010-09-15
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C04US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C04US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☒ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☒ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C04US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
● Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	SYNERGY PHARMACEUTICALS, INC.		
Mailing Address Information For Applicant:			
Address 1	420 Lexington Avenue		
Address 2	Suite 2012		
City	New York	**State/Province**	NY
Country	US	Postal Code	10170
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C04US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Anne E. Fleckenstein/			Date (YYYY-MM-DD)	2017-03-23
First Name	Anne E.	Last Name	Fleckenstein	Registration Number	62951

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C04US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

RELATED APPLICATIONS

[01] This application is a continuation of U.S. Patent Application No. 14/845,644 filed September 4, 2015, now U.S. Patent No. 9,610,321, which is a continuation of U.S. Patent Application No. 14/661,299, filed March 18, 2015, which is a continuation of U.S. Patent Application No. 13/421,769, filed March 15, 2012, which is a continuation-in-part of PCT/US2011/051805 filed on September 15, 2011, which claims the benefit of priority to U.S. Provisional Application No. 61/383,156 filed on September 15, 2010, U.S. Provisional Application No. 61/387,636 filed on September 29, 2010, and U.S. Provisional Application No. 61/392,186 filed on October 12, 2010, the contents of which are incorporated by reference in their entireties.

INCORPORATION-BY-REFERENCE OF SEQUENCE LISTING

[02] The contents of the text file named "SYPA_009_C04US_Sequence_Listing.txt", which was created on March 23, 2017 and is 113 KB in size, are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[03] The present invention relates to low-dose formulations of guanylate cyclase C peptide agonists useful for the treatment and prevention of various diseases and disorders.

BACKGROUND OF THE INVENTION

[04] Guanylate cyclase C is a transmembrane form of guanylate cyclase that is expressed on various cells, including gastrointestinal epithelial cells (reviewed in Vaandrager 2002 *Mol. Cell. Biochem.* 230:73-83). It was originally discovered as the intestinal receptor for the heat-stable toxin (ST) peptides secreted by enteric bacteria and which cause diarrhea. The ST peptides share a similar primary amino acid structure with two peptides isolated from intestinal mucosa and urine, guanylin and uroguanylin (Currie, *et al.*, *Proc. Nat'l Acad. Sci. USA 89*:947-951 (1992); Hamra, *et al.*, *Proc. Nat'l Acad. Sci. USA 90*:10464-10468 (1993);

Forte, L., *Reg. Pept. 81*:25-39 (1999); Schulz, *et al.*, *Cell 63*:941-948 (1990); Guba, *et al.*, *Gastroenterology 111*:1558-1568 (1996); Joo, *et al.*, *Am. J. Physiol. 274*:G633-G644 (1998)).

[05] In the intestines, guanylin and uroguanylin act as regulators of fluid and electrolyte balance. In response to high oral salt intake, these peptides are released into the intestinal lumen where they bind to guanylate cyclase C localized on the luminal membrane of enterocytes (simple columnar epithelial cells of the small intestines and colon). The binding of the guanylin peptides to guanylate cyclase C induces electrolyte and water excretion into the intestinal lumen via a complex intracellular signaling cascade that is initiated by an increase in cyclic guanosine monophosphate (cGMP).

[06] The cGMP-mediated signaling that is initiated by the guanylin peptides is critical for the normal functioning of the gut. Any abnormality in this process could lead to gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammatory bowel diseases. Inflammatory bowel disease is a general name given to a group of disorders that cause the intestines to become inflamed, characterized by red and swollen tissue. Examples include ulcerative colitis and Crohn's disease. Crohn's disease is a serious inflammatory disease that predominantly affects the ileum and colon, but can also occur in other sections of the gastrointestinal tract. Ulcerative colitis is exclusively an inflammatory disease of the colon, the large intestine. Unlike Crohn's disease, in which all layers of the intestine are involved, and in which there can be normal healthy bowel in between patches of diseased bowel, ulcerative colitis affects only the innermost lining (mucosa) of the colon in a continuous manner. Depending on which portion of the gastrointestinal tract is involved, Crohn's disease may be referred to as ileitis, regional enteritis, colitis, etc. Crohn's disease and ulcerative colitis differ from spastic colon or irritable bowel syndrome, which are motility disorders of the gastrointestinal tract. Gastrointestinal inflammation can be a chronic condition. It is estimated that as many as 1,000,000 Americans are afflicted with inflammatory bowel disease, with male and female patients appearing to be equally affected. Most cases are diagnosed before age 30, but the disease can occur in the sixth, seventh, and later decades of life.

[07] IBS and chronic idiopathic constipation are pathological conditions that can cause a great deal of intestinal discomfort and distress but unlike the inflammatory bowel diseases, IBS does not cause the serious inflammation or changes in bowel tissue and it is not thought

to increase the risk of colorectal cancer. In the past, inflammatory bowel disease, celiac disease and IBS were regarded as completely separate disorders. Now, with the description of inflammation, albeit low-grade, in IBS, and of symptom overlap between IBS and celiac disease, this contention has come under question. Acute bacterial gastroenteritis is the strongest risk factor identified to date for the subsequent development of postinfective irritable bowel syndrome. Clinical risk factors include prolonged acute illness and the absence of vomiting. A genetically determined susceptibility to inflammatory stimuli may also be a risk factor for irritable bowel syndrome. The underlying pathophysiology indicates increased intestinal permeability and low-grade inflammation, as well as altered motility and visceral sensitivity. Serotonin (5-hydroxytryptamine [5-HT]) is a key modulator of gut function and is known to play a major role in pathophysiology of IBS. The activity of 5-HT is regulated by cGMP.

[08] While the precise causes of IBS and inflammatory bowel diseases (IBD) are not known, a disruption in the process of continual renewal of the gastrointestinal mucosa may contribute to disease pathology in IBD and aggravate IBS. The renewal process of the gastrointestinal lining is an efficient and dynamic process involving the continual proliferation and replenishment of unwanted damaged cells. Proliferation rates of cells lining the gastrointestinal mucosa are very high, second only to the hematopoietic system. Gastrointestinal homeostasis depends on both the proliferation and programmed cellular death (apoptosis) of epithelial cells lining the gut mucosa. Cells are continually lost from the villus into the lumen of the gut and are replenished at a substantially equal rate by the proliferation of cells in the crypts, followed by their upward movement to the villus. The rates of cell proliferation and apoptosis in the gut epithelium can be increased or decreased in a variety of circumstances, *e.g.*, in response to physiological stimuli such as aging, inflammatory signals, hormones, peptides, growth factors, chemicals and dietary habits. In addition, an enhanced proliferation rate is frequently associated with a reduction in turnover time and an expansion of the proliferative zone. The proliferation index is much higher in pathological states such as ulcerative colitis and other gastrointestinal disorders. Intestinal hyperplasia is a major promoter of gastrointestinal inflammation. Apoptosis and cell proliferation together regulate cell number and determine the proliferation index. Reduced rates of apoptosis are often associated with abnormal growth, inflammation, and neoplastic transformation. Thus, both increased proliferation and/or reduced cell death may increase the

proliferation index of intestinal tissue, which may in turn lead to gastrointestinal inflammatory diseases.

[09] In addition to a role for uroguanylin and guanylin as modulators of intestinal fluid and ion secretion, these peptides may also be involved in the continual renewal of gastrointestinal mucosa by maintaining the balance between proliferation and apoptosis. For example, uroguanylin and guanylin peptides appear to promote apoptosis by controlling cellular ion flux. Given the prevalence of inflammatory conditions in Western societies a need exists to improve the treatment options for inflammatory conditions, particularly of the gastrointestinal tract.

[10] Peptide agonists of guanylate cyclase C agonists ("GCC agonists") are described in U.S. Patent Nos. 7,041,786, 7,799,897, and U.S. Patent Application Publication Nos. US2009/0048175, US 2010/0069306, US 2010/0120694, US 2010/0093635, and US 2010/0221329. However, the formulation of peptides for pharmaceutical delivery presents a number of special problems. For example, peptides are subject to structural modifications by a variety of degradation mechanisms resulting in problems of chemical and physical instability of the formulation.

SUMMARY OF THE INVENTION

[11] The present invention provides low-dose formulations of peptide agonists of guanylate cyclase C ("GCC") and methods for their use in the treatment and prevention of human diseases and disorders, such as a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction; Crohn's disease, ulcerative colitis, inflammatory bowel disease, colonic pseudo-obstruction, obesity, congestive heart failure, and benign prostatic hyperplasia. In certain embodiments, the formulations are stabilized against chemical degradation of the peptide. The low-dose formulations of the invention have unexpected efficacy in humans in a dosage range that was not predicted based on studies in primates. The formulations of the invention are particularly useful for the treatment or prevention of chronic idiopathic constipation. In certain embodiments, the GCC agonists are analogs of uroguanylin and bacterial ST peptides. In preferred embodiments, the

analogs have superior properties compared to the naturally occurring or "wild-type" peptides. Examples of such superior properties include a high resistance to degradation at the N-terminus and C-terminus from carboxypeptidases, aminopeptidases, and/or by other proteolytic enzymes present in the stimulated human intestinal juices and human gastric juices. Examples of GCC agonists that can be used in the formulations and methods of the invention are described in more detail below and in U.S. Patent Nos. 7,041,786, 7,799,897, and U.S. Patent Application Publication Nos. US2009/0048175, US 2010/0069306, US 2010/0120694, US 2010/0093635, and US 2010/0221329, each of which is incorporated herein by reference in its entirety.

[12] The invention provides an oral dosage formulation comprising one or more pharmaceutically acceptable excipients and at least one GCC agonist peptide, wherein the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg, and wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1-54 and 56-249. In one embodiment, the GCC agonist peptide has a chromatographic purity of no less than 90%, no less than 90.5%, no less than 91%, no less than 92%, no less than 93%, no less than 94%, no less than 95%, no less than 96%, no less than 97%, no less than 98%, or no less than 99%. The chromatographic purity of the GCC agonist peptide is determined as area percent by HPLC. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, or 56. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1 and 9. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 8 and 9. In one embodiment, the amount of GCC agonist peptide per unit dose is 0.1 mg, 0.3 mg, 0.6 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg or 9.5 mg.

[13] In one embodiment, the GCC agonist peptide has a total impurity content of no greater than 10%, no greater than 9.5%, no greater than 9%, no greater than 8%, no greater than 7%, no greater than 6%, no greater than 5%, no greater than 4%, no greater than 3%, no greater than 2%, or no greater than 1%. The total impurity content is determined as total area percentages of impurities by HPLC. The impurities do not include any pharmaceutically acceptable excipient used for the formulation. In one embodiment, the formulation is substantially free of inorganic acids and carboxylic acids, e.g., HCl, phosphoric acid, or acetic acid. In this context, carboxylic acids do not include amino acids or peptides. In this context "substantially" free of acids means that the acid content of the formulation at the time

of packaging is preferably less than 0.2%, less than 0.1%, less than 0.05%, less than 0.01%, less than 0.005%, or less than 0.001% of the total weight of the formulation. In one embodiment, the formulation is free of HCl.

[14] In one embodiment, the formulation is a solid formulation. In one embodiment, the formulation is in the form of a powder, granule, sachet, troche, tablet, or capsule. In another embodiment, the formulation is a liquid formulation and the GCC agonist peptide is in solution or suspension in a lipophilic liquid. In one embodiment, the liquid is a refined specialty oil or a medium chain triglyceride or related ester. In one embodiment, the refined specialty oil is selected from Arachis oil, Castor oil, cottonseed oil, maize (corn) oil, olive oil, sesame oil, soybean oil, and sunflower oil. In one embodiment, the medium chain triglyceride or related ester is AKOMED E, AKOMED R, CAPTEX 355, LABRAFAC CC, LABRAFAC PG, LAUROGLYCOL FCC, MIGLYOL 810, MIGLYOL 812, MIGLYOL 829, MIGLYOL 840, and SOFTISAN 645. In one embodiment, the liquid is selected from the group consisting of medium chain triglycerides, propylene glycol dicaprylocaprate, vitamin E, soybean oil, Cremaphor, PG, and PG 400. In one embodiment, the unit dose is a powder, tablet, or capsule. In one embodiment, the unit dose is a liquid-filled capsule. In one embodiment, the capsule or tablet is in a blister pack or strip. Preferably, the blister pack or strip is made of a material that is impermeable to water vapor and oxygen. In one embodiment the blister pack is comprised of a metal foil. In one embodiment the blister pack is a FOIL/FOIL blister pack. In one embodiment, the container of the blister pack is flushed with an inert gas such as nitrogen or argon. In one embodiment, the container further includes a desiccant. In a preferred embodiment the desiccant is a molecular sieve. In one embodiment, the unit dose is in a high density polyethylene bottle having a seal. In one embodiment, the bottle further comprises a desiccant. In one embodiment, the bottle further comprises an oxygen scavenger or molecular sieve. In one embodiment, the bottle is nearly impermeable to oxygen and water vapor (e.g., much more impermeable than a HDPE bottle), such as an OxyGuard bottle.

[15] In one embodiment, the one or more pharmaceutically acceptable excipients include an inert carrier. In one embodiment, the inert carrier is a selected from mannitol, lactose, a microcrystalline cellulose, or starch. In one embodiment, the inert carrier has a particle size of from 50 to 900 microns, from 50 to 800 microns, from 50 to 300 microns, from 50 to 200 microns, from 75 to 150 microns, from 75 to 200 microns, or from 75 to 300 microns.

[16] In one embodiment, the GCC agonist peptide is stabilized against chemical or physical degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

[17] In one embodiment, the one or more pharmaceutically acceptable excipients include a divalent cation salt such as calcium chloride. In one embodiment, the one or more pharmaceutically acceptable excipients comprise an amino acid, such as leucine, histidine, or arginine, or an amine such TRIS or TRIS/HCl.

[18] In one embodiment, the oral dosage formulation consists of the GCC agonist peptide described herein, an inert carrier (e.g., Celphere SCP-100, Avicel PH 102, or Avicel PH 112), and a lubricant (e.g., magnesium stearate). In one embodiment, the formulation consists of the GCC agonist peptide, an inert carrier (e.g., Avicel PH 200), a divalent cation salt (e.g., calcium chloride or calcium ascorbate), an amino acid (e.g., leucine, histidine, or arginine) or a protective amine (e.g., TRIS), a coating agent (e.g., Methocel ES Premium LV) and optionally a lubricant (e.g., magnesium stearate) or another additive (e.g., trehalose). In one embodiment, the formulation consists of the GCC agonist peptide, a binder (e.g., Provsolv SMCC 90 LM), and a disintegrant (e.g., Explotab). In one embodiment, the formulation consists of the GCC agonist peptide, a diluent (e.g., Mannogem EZ), a binder (e.g., Provsolv SMCC 90 LM), a disintegrant (e.g., Explotab), a lubricant (e.g., Pruv).

[19] The invention also provides a process for making the oral dosage formulations described herein, wherein the process comprises a step of dry granulation, wet granulation, or spray coating followed by drying. In another embodiment, the process comprises a step of dry mixing. In a preferred embodiment the step of dry mixing includes geometric blending. In one embodiment, the process comprises a step of direct compression. In one embodiment, the process for making the oral dosage formulations described herein is a spray coating-drying process which includes (a) providing an aqueous solution comprising: a GCC agonist peptide selected from the group consisting of SEQ ID NOs: 1-54 and 56-249, and one or more pharmaceutically acceptable excipients, wherein the concentration of the GCC agonist peptide ranges from 10 to 60 mg/mL; and (b) applying the aqueous solution to a pharmaceutically acceptable carrier to generate a GCC agonist peptide-coated carrier.

[20] In one embodiment of the spray coating-drying process above, the one or more pharmaceutically acceptable excipients comprise a divalent cation salt wherein the divalent

cation is selected from Ca^{2+}, Mg^{2+}, Zn^{2+}, and Mn^{2+}. In one embodiment, the one or more pharmaceutically acceptable excipients comprise an amino acid selected from leucine, isoleucine, and valine. In one embodiment, the one or more pharmaceutically acceptable excipients comprise a coating agent (such as hypromellose Methocel E5 PremLV). In one embodiment, the aqueous solution has a pH greater than 4 (e.g., 4.5-5.5, 5-6, about 5, or greater than 5) or even greater than 7. In one embodiment, the aqueous solution is substantially free of inorganic acids and carboxylic acids. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, and 56. In one embodiment, the process further includes drying the GCC agonist peptide-coated carrier.

[21] The invention further provides an oral dosage formulation made by the process described herein. Preferably, the GCC agonist peptide as made is stabilized against chemical or physical degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

[22] The invention also provides a method for treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject an oral dosage formulation comprising at least one GCC agonist peptide, wherein the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg, and wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1-54 and 56-249. Preferably, the subject is a human subject. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, or 56. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1 and 9. In one embodiment, the amount of GCC agonist peptide per unit dose is 0.1 mg, 0.3 mg, 0.6 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg, 9.5 mg, or 10 mg.

[23] In one embodiment, the disease or disorder is a gastrointestinal disease or disorder selected from the group consisting of irritable bowel syndrome, non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastro esophageal reflux disease, constipation, gastroparesis, heartburn, gastric cancer, and H. pylori infection. In a preferred embodiment, the gastrointestinal disease or disorder is chronic idiopathic constipation.

[24] In one embodiment, the method further comprises administering to the subject an effective amount of an inhibitor of a cGMP-specific phosphodiesterase. In one embodiment,

the cGMP-dependent phosphodiesterase inhibitor is selected from the group consisting of suldinac sulfone, zaprinast, and motapizone, vardenifil, and suldenifil.

[25] In one embodiment, the method further comprises administering to the subject an effective amount of at least one laxative. In one embodiment, the at least one laxative is selected from the group consisting of SENNA, MIRALAX, PEG, or calcium polycarbophil.

[26] In one embodiment, the method further comprises administering to the subject an effective amount of at least one anti-inflammatory agent.

[27] The invention also provides pharmaceutical compositions comprising the formulations described herein.

[28] Other features and advantages of the invention will be apparent from and are encompassed by the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[29] Figure 1: Plecanatide (SP-304) treatment reduced time to first BM following daily dose.

[30] Figure 2: Effect of daily treatment with plecanatide on spontaneous bowel movements (SBM) in chronic constipation patients.

[31] Figure 3: Effect of daily treatment with plecanatide on complete spontaneous bowel movements (CSBM) in chronic constipation patients.

[32] Figure 4: Effect of daily treatment with plecanatide on Bristol Stool Form Scores (BSFS) in chronic constipation patients.

[33] Figure 5: Effect of daily treatment with plecanatide on straining scores in chronic constipation patients

[34] Figure 6: Percentage of subjects reporting improvements in abdominal discomfort scores after 14-days of daily treatment with plecanatide.

DETAILED DESCRIPTION

[35] The invention provides pharmaceutical formulations of peptide GCC agonists. It is intended that the formulations of the invention are "pharmaceutical" formulations, meaning that they are suitable for pharmaceutical use. Accordingly, the term "formulations" as used herein is meant to encompass pharmaceutical formulations even if "pharmaceutical" is not expressly stated. Pharmaceutical compositions comprising the formulations described herein are also provided by the invention. The formulations of the invention preferably provide stability against chemical and physical degradation of the peptide, e.g., plecanatide (i.e., SEQ ID #1).

[36] The invention is based in part upon the discovery that mannitol mixes very effectively with the GCC agonist peptides described herein and provides stability against degradation, allowing the peptides to be formulated at very low doses. The invention is also based in part on the discovery that very low doses of the GCC agonist peptides described herein are effective for the treatment of diseases and disorders in humans. The dosage range found to be effective was not predicted based on animal studies. The invention is also based in part upon the discovery that a divalent cation (e.g., Ca^{2+}) and/or an amino acid (e.g., leucine or arginine) stabilize the GCC agonist peptides described herein during a process (e.g., spray coating-drying process) of manufacturing a formulation of the GCC agonist peptides and provides stability against degradation both during the manufacturing process and storage of the formulation.

[37] Plecanatide is a charged peptide due to the presence of four carboxylic acids and single amine group with a calculated pKa of approximately 3.5. Therefore plecanatide is likely to interact with ions in solution or in the solid state. Plecanatide is a hygroscopic peptide requiring the control of water during manufacture and storage to promote long term stability. Plecanatide is prone to degradation by oxidation in the presence of residual peroxides or formaldehyde contaminants that are formed from peroxide reaction with polymeric excipients. The present invention discloses a manufacturing process and dry solid formulation compositions that minimizes water content. The formulations are comprised of components to minimize levels of residual formaldehyde and peroxides commonly found in many pharmaceutical excipients. The invention also discloses additives (i.e. $CaCl_2$) that may function as local desiccants in the formulation. Divalent cation salts such as calcium

ascorbate, $MgCl_2$, $ZnCl_2$, $MnCl_2$ and $CaCl_2$ bind plecanatide and sterically hinder reactive species such as water or oxygen from causing plecanatide degradation by molecular displacement. The invention further includes scavengers of residual formaldehyde (amines such as TRIS or TRIS/HCl or amino acids such as leucine, isoleucine and valine), and discloses packaging confirmations to minimize oxygen exposure and water vapor during storage. The invention also discloses a stable manufacturing process comprised of initially dissolving plecanatide in cold water to minimize solution degradation, followed by spray coating the peptide solution on particles and drying to remove moisture.

[38] The formulations of the invention are particularly useful for the treatment or prevention of a gastrointestinal disease or disorder selected from the group consisting of irritable bowel syndrome, non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastro esophageal reflux disease, chronic idiopathic constipation, gastroparesis, heartburn, gastric cancer, and H. pylori infection.

[39] In one embodiment, the formulations of the invention are used in a method for the treatment of constipation. Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining. Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease and cystic fibrosis. Constipation may also be the result of surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics. In a preferred embodiment, the constipation is chronic idiopathic constipation.

[40] The stabilized formulations of the invention comprise at least one GCC agonist peptide formulated with one or more excipients such that the peptide is stabilized against chemical degradation. Chemical degradation of peptides results from a number of mechanisms including oxidation, water-mediated degradation, and reaction with aldehydes or

reducing sugars. The ideal excipient or combination of excipients will be non-hygroscopic, have few or no reducing sugars, and be substantially free of contaminants such as iron, peroxide, and formaldehyde. The formulations of the invention are preferably substantially free of water. In this context "substantially" free of water means that the water content of the formulation at the time of packaging is preferably less than 7%, less than 5%, less than 1%, or less than 0.5% of the total weight of the formulation. In one embodiment the amount of water is between 0.1 to 5% of the total weight of the formulation. In one embodiment, the amount of water in the formulation of the invention manuafactured through a spray-coating process is less than 0.5% (e.g., about 0.47%).

[41] In the context of the present formulations, the term "stable" or "stabilized" refers to the resistance of the peptide to chemical or physical degradation over time. Preferably, a stable formulation of the invention retains an amount of the peptide in the formulation over a period of time that is at least 90%, preferably at least 95%, and most preferably at least 99% the amount of peptide initially present in the formulation. In one embodiment, a stable formulation of the invention, over a period of time (e.g., 18 month), has an increase in the total impurity content not greater than 8%, not greater than 7%, not greater than 6%, not greater than 5%, not greater than 4%, not greater than 3%, not greater than 2%, or not greater than 1%. In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 18 months, at least 20 months, or at least 24 months when stored at 25 degrees Celsius (25C) and 60 % relative humidity. In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 18 months, at least 20 months, or at least 24 months when stored at 2-8 degrees Celsius (2-8C). In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 3 months, 12 months, 18 months and preferably 24 months when stored at 25 degrees Celsius (25C) and 60 % relative humidity. In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 3 months, 18 months and preferably 24 months when stored at 30 degrees Celsius (30C).

[42] The low-dose formulations of the invention comprise an amount of at least one GCC agonist peptide per unit dose that is less than 10 mg. It is especially advantageous to formulate oral compositions in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage form" as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity

of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved. In one embodiment, the unit dosage form is a tablet or a capsule.

[43] In one embodiment of the low-dose formulations of the invention, the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg. In one embodiment, the amount of GCC agonist peptide per unit dose is 0.1 mg, 0.3 mg, 0.6 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg, 9.5 mg, or 10 mg.

[44] In one embodiment, the low-dose formulation contains a carrier that is non-hygroscopic. In one embodiment, the carrier is selected from mannitol and maltose (e.g., ADVANTOSE 100).

[45] In one embodiment, the carrier is cellulose, preferably microcrystalline cellulose (e.g., Avicel PH 102, low moisture Avicel PH 112, Avicel PH 200, or Celphere SCP-100). In one embodiment, the carrier is calcium phosphate or calcium sulphate. In another embodiment, the carrier is a saccharide. The term "saccharide" as used herein also refers to polysaccharides. Thus, the term saccharide is meant to include polysaccharides. In one embodiment, the saccharide is selected from mannitol, trehalose, lactose, sucrose, sorbitol, and maltose. In a preferred embodiment, the saccharide is mannitol. Preferably the saccharide has a low water content, a small particle size and a narrow particle-size distribution.

[46] Carriers having small particle sizes, and/or spherical shape, and narrow size distribution are preferred. Particles of less than 20 microns have a relatively high surface area to volume ratio causing inter-particle attractive forces to dominate and resist bulk flow. Larger particles (greater than 100 microns) tend to roll or slide over one another and exhibit superior bulk flow properties compared with small particles. A narrow particle-size distribution reduces particle packing and increases flow. In one embodiment, the particles are between 20 and 500 microns in size (as measured across the largest diameter of the particle, on average). In one embodiment, a small particle size and a narrow particle size range refers to particles having a size range of from 20-300 microns, 50-200 microns, or 75-

150 microns. In certain embodiments, the carrier has a substantially spherical shape such as can be obtained with a spray drying process.

[47] In one embodiment, the low-dose formulation is a solid formulation and the unit dose is in the form of a tablet or capsule. In one embodiment, the low-dose formulation is a liquid formulation and the unit dosage form is a liquid-filled capsule. In one embodiment, the liquid formulation in the form of a solution or suspension of the GCC agonist peptide in an lipophilic liquid. Examples of suitable liquids include medium chain triglycerides (e.g., LABRAFAC Lipophile), propylene glycol dicaprylocaprate (e.g., LABRAFAC PG), vitamin E (e.g., α tocopherol), PEG 400 (e.g., Polyethylene glycol low M.W. (liquid)), propylene glycol, soybean oil, and Castor oil. In one embodiment, the liquid is selected from the group consisting of medium chain triglycerides, propylene glycol dicaprylocaprate, vitamin E, and soybean oil. In one embodiment, the refined specialty oil is selected from Arachis oil, Castor oil, cottonseed oil, maize (corn) oil, olive oil, sesame oil, soybean oil, and sunflower oil. In one embodiment, the medium chain triglyceride or related ester is AKOMED E, AKOMED R, CAPTEX 355, LABRAFAC CC, LABRAFAC PG, LAUROGLYCOL FCC, MIGLYOL 810, MIGLYOL 812, MIGLYOL 829, MIGLYOL 840, and SOFTISAN 645.

[48] A formulation according to the invention may be contained in a blister pack. In a particular embodiment, the powder, tablet, or capsule comprising the formulation is contained in a blister pack. Preferably, the blister pack is made of a material that allows only minimal permeation by water vapor and oxygen. In one embodiment the blister pack is comprised of a metal foil. In one embodiment, the blister pack is comprised of ACLAR. In one embodiment, the container of the blister pack is flushed with an inert gas such as nitrogen or argon. In one embodiment, the container further includes a desiccant. In one embodiment, the desiccant is calcium chloride. In one embodiment the desiccant is a molecular sieve.

[49] While any GCC agonist known in the art can be formulated according to the present invention, analogs of uroguanylin and bacterial ST peptides are preferred. In certain embodiments, the uroguanylin and bacterial ST peptide analogs have superior properties compared to naturally occurring, or "wild-type" peptides. For example, the uroguanylin and bacterial ST peptides for use in the present invention are preferably modified to increase their resistance to degradation at the N-terminus and C-terminus from carboxypeptidases, aminopeptidases, and/or by other proteolytic enzymes present in the stimulated human

intestinal juices and human gastric juices. In certain embodiments, the GCC agonist formulation comprises a peptide consisting essentially of an amino acid sequence selected from SEQ ID NOs: 1-249. In a preferred embodiment, the peptide consists essentially of an amino acid sequence selected from SEQ ID NOs: 1, 8, 9, 55 and 56. The term "consists essentially of" refers to a peptide that is identical to the reference peptide in its amino acid sequence or to a peptide that does not differ substantially in terms of either structure or function from the reference peptide. A peptide differs substantially from the reference peptide if its primary amino acid sequence varies by more than three amino acids from the reference peptide or if its activation of cellular cGMP production is reduced by more than 50% compared to the reference peptide. Preferably, substantially similar peptides differ by no more than two amino acids and not by more than about 25% with respect to activating cGMP production. In preferred embodiments, the GCC agonist is a peptide comprising at least 12 amino acid residues, and most preferably comprising between 12 and 26 amino acids. Non-limiting examples of such analogs of uroguanylin and bacterial ST peptides are described in Section 1.2 below.

[50] The invention provides methods for treating or preventing certain diseases and disorders and methods for increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. The term "treating" as used herein refers to a reduction, a partial improvement, amelioration, or a mitigation of at least one clinical symptom associated with the gastrointestinal disorders being treated. The term “preventing” refers to an inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorders to be prevented. The term "effective amount” as used herein refers to an amount that provides some improvement or benefit to the subject. In certain embodiments, an effective amount is an amount that provides some alleviation, mitigation, and/or decrease in at least one clinical symptom of the gastrointestinal disorder to be treated. In other embodiments, the effective amount is the amount that provides some inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorder to be prevented. The therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject. The term “subject” preferably refers to a human subject but may also refer to a non-human primate or other mammal preferably selected from among a mouse, a rat, a dog, a cat, a cow, a horse, or a pig.

[51] In accordance with the methods of the present invention, the GCC agonist formulation can be administered alone or in combination with one or more additional therapeutic agents to prevent or treat inflammation, cancer and other disorders, particularly of the gastrointestinal tract. In a preferred embodiment, the GCC agonist formulation is administered for the treatment of chronic constipation. In one embodiment, the GCC agonist formulation is administered in combination with one or more additional therapeutic agents selected from the group consisting of phosphodiesterase inhibitors, cyclic nucleotides (such as cGMP and cAMP), a laxative (such as SENNA, METAMUCIL, MIRALAX, PEG, or calcium polycarbophil), a stool softener, an anti-tumor necrosis factor alpha therapy for IBD (such as REMICADE, ENBREL, or HUMAIRA), and anti-inflammatory drugs (such as COX-2 inhibitors, sulfasalazine, 5-ASA derivatives and NSAIDS). In certain embodiments, the GCC agonist formulation is administered in combination with an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said GCC agonist. cGMP-PDE inhibitors include, for example, suldinac sulfone, zaprinast, motapizone, vardenifil, and sildenafil. In another embodiment, the GCC agonist formulation is administered in combination with inhibitors of cyclic nucleotide transporters.

1.1 Formulations

[52] The formulations of the invention contain one or more GCC agonist peptides described herein, in combination with one or more pharmaceutically acceptable carriers (also referred to as diluents) and/or excipients. In a preferred embodiment, the formulations of the invention include an inert carrier. The inert carrier is preferably non-hygroscopic. In one embodiment, the carrier in the formulation contains few or no reducing sugars and is substantially free of contaminants including, but not limited to, iron, peroxide, and formaldehyde. In one embodiment, the carrier is selected from the group consisting of sorbitol, mannitol, EMDEX, and starch. In one embodiment, the carrier is mannitol (e.g., MANNOGEM) or microcrystalline cellulose (e.g. PROSOLV, CELPHERE, CELPHERE beads).

[53] The low-dose formulations of the invention contain no greater than 10 mg per unit dose of a GCC agonist peptide. The remainder of the formulation is comprised of the carrier and one or more optional excipients. In one embodiment, the amount of carrier is at least

90% of the total weight of the formulation. In another embodiment, the amount of carrier is at least 95% or at least 98% of the total weight of the formulation. In one embodiment, the amount of carrier is between 90 and 99.9% of the total weight of the formulation. In one embodiment, the one or more optional excipients comprise a disintegrant which is present at 1 to 5% of the total weight of the formulation. In one embodiment, the one or more optional excipients comprise a lubricant which is present at 0.02 to 5% of the total weight of the formulation. In one embodiment, the one or more optional excipients comprise an amino acid such as arginine, leucine, isoleucine, valine, histidine, phenylalanine, alanine, glutamic acid, aspartic acid, glutamine, methionine, asparagine, tyrosine, threonine, tryptophan, or glycine, which is present at 0.1 to 4% (e.g., 0.1-1%) of the total weight of the formulation. In one embodiment, the molar ratio between the amino acid and the GCC agonist peptide is from about 2:1 to about 30:1 or about 2:1 to about 20:1 (e.g., 5:1). In one embodiment, the one or more optional excipients comprise a stabilizer such as a divalent cation salt, more specifically, a water-soluble divalent cation salt (e.g., calcium chloride, magnesium chloride, zinc chloride, manganese chloride, or calcium ascorbate), which is present at 0.1 to 12% (e.g., 0.1-4%) of the total weight of the formulation. In one embodiment, the molar ratio between the salt and the GCC agonist peptide is from about 5:1 to about 20:1 (e.g., 10:1).

[54] The formulations may contain other additives as needed, including for example lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffnose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and polypeptides and proteins, for example albumen.

[55] Further examples of pharmaceutically acceptable carriers and excipients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, antioxidant, and coating agents such as: BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, xanthan, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone (e.g., povidone, crospovidone, copovidone, etc), methyl cellulose, Methocel, pre-gelatinized starch (e.g., STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (FMC Corporation, Marcus Hook, PA, USA), Emdex, Plasdone, or mixtures thereof, FILLERS:

talc, calcium carbonate (e.g., granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, dextrose, fructose, honey, lactose anhydrate, lactose monohydrate, lactose and aspartame, lactose and cellulose, lactose and microcrystalline cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose & guar gum, molasses, sucrose,or mixtures thereof, DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate (such as Explotab), potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums (like gellan), low-substituted hydroxypropyl cellulose, ploy plasdone, or mixtures thereof, LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, compritol, stearic acid, sodium lauryl sulfate, sodium stearyl fumarate (such as Pruv), vegetable based fatty acids lubricant, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Piano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof, ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof, ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof, ANTOXIDANTS: ascorbic acid, BHA, BHT, EDTA, or mixture thereof, and COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, gellan gum, maltodextrin, methacrylates, microcrystalline cellulose and carrageenan or mixtures thereof.

[56] The formulation can also include other excipients and categories thereof including but not limited to Pluronic®, Poloxamers (such as Lutrol® and Poloxamer 188), ascorbic acid, glutathione, protease inhibitors (e.g. soybean trypsin inhibitor, organic acids), pH lowering agents, creams and lotions (like maltodextrin and carrageenans); materials for chewable tablets (like dextrose, fructose, lactose monohydrate, lactose and aspartame, lactose and cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose and guar gum, sorbitol crystalline); parenterals (like mannitol and povidone); plasticizers (like dibutyl sebacate, plasticizers for coatings, polyvinylacetate phthalate); powder lubricants (like glyceryl behenate); soft gelatin capsules (like sorbitol special solution); spheres for coating (like sugar spheres); spheronization agents (like glyceryl behenate and microcrystalline cellulose); suspending/gelling agents (like carrageenan, gellan gum, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, xanthan gum); sweeteners (like aspartame, aspartame and lactose, dextrose, fructose, honey, maltodextrin, maltose, mannitol, molasses, sorbitol crystalline, sorbitol special solution, sucrose); wet granulation agents (like calcium carbonate, lactose anhydrous, lactose monohydrate, maltodextrin, mannitol, microcrystalline cellulose, povidone, starch), caramel, carboxymethylcellulose sodium, cherry cream flavor and cherry flavor, citric acid anhydrous, citric acid, confectioner's sugar, D&C Red No. 33, D&C Yellow #10 Aluminum Lake, disodium edetate, ethyl alcohol 15%, FD&C Yellow No. 6 aluminum lake, FD&C Blue # 1 Aluminum Lake, FD&C Blue No. 1, FD&C blue no. 2 aluminum lake, FD&C Green No.3, FD&C Red No. 40, FD&C Yellow No. 6 Aluminum Lake, FD&C Yellow No. 6, FD&C Yellow No.10, glycerol palmitostearate, glyceryl monostearate, indigo carmine, lecithin, manitol, methyl and propyl parabens, mono ammonium glycyrrhizinate, natural and artificial orange flavor, pharmaceutical glaze, poloxamer 188, Polydextrose, polysorbate 20, polysorbate 80, polyvidone, pregelatinized corn starch, pregelatinized starch, red iron oxide, saccharin sodium, sodium carboxymethyl ether, sodium chloride, sodium citrate, sodium phosphate, strawberry flavor, synthetic black iron oxide, synthetic red iron oxide, titanium dioxide, and white wax.

[57] Solid oral dosage forms may optionally be treated with coating systems (e.g. Opadry® fx film coating system, for example Opadry® blue (OY-LS-20921), Opadry® white (YS-2-7063), Opadry® white (YS- 1-7040), and black ink (S- 1-8 106).

[58] The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycoloic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO

01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ε-caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Other sustained release formulations and polymers for use in the compositions and methods of the invention are described in EP 0 467 389 A2, WO 93/24150, U.S. 5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 97/26015, WO 97/04744, and US20020019446. In such sustained release formulations microparticles (Delie and Blanco-Prieto 2005 Molecule 10:65-80) of polypeptide are combined with microparticles of polymer. U.S. 6,011,0 1 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (i.e. PEG 300 and PEG 400) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled releaseof the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1, U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224 materials which may include those described in WO04041195 (including the seal and enteric coating described therein) and pH-sensitive coatings that achieve delivery in the colon including those described in US4,910,021 and WO9001329. US4910021 describes using a pH-sensitive material to coat a capsule. WO9001329 describes using pH-sensitive coatings on beads containing acid, where the acid in the bead core prolongs dissolution of the pH-sensitive coating. U. S. Patent No. 5,175,003 discloses a dual mechanism polymer mixture composed of pH-sensitive enteric materials and film-forming plasticizers capable of conferring permeability to the enteric material, for use in drug-delivery systems; a matrix pellet composed of a dual mechanism polymer mixture permeated with a drug and sometimes covering a pharmaceutically neutral nucleus; a membrane- coated pellet comprising a matrix pellet coated with a dual mechanism polymer mixture envelope of the same or different composition; and a pharmaceutical dosage form containing matrix pellets. The matrix pellet releases acid-soluble drugs by diffusion in acid pH and by disintegration at pH levels of nominally about 5.0 or higher.

[59] The GCC peptides described herein may be formulated in the pH triggered targeted control release systems described in WO04052339. The agents described herein may be

formulated according to the methodology described in any of WO03105812 (extruded hyrdratable polymers); WO0243767 (enzyme cleavable membrane translocators); WO03007913 and WO03086297 (mucoadhesive systems); WO02072075 (bilayer laminated formulation comprising pH lowering agent and absorption enhancer); WO04064769 (amidated polypeptides); WO05063156 (solid lipid suspension with pseudotropic and/or thixotropic properties upon melting); WO03035029 and WO03035041 (erodible, gastric retentive dosage forms); US5007790 and US5972389 (sustained release dosage forms); WO041 1271 1 (oral extended release compositions); WO05027878, WO02072033, and WO02072034 (delayed release compositions with natural or synthetic gum); WO05030182 (controlled release formulations with an ascending rate of release); WO05048998 (microencapsulation system); US Patent 5,952,314 (biopolymer); US5,108,758 (glassy amylose matrix delivery); US 5,840,860 (modified starch based delivery). JP10324642 (delivery system comprising chitosan and gastric resistant material such as wheat gliadin or zein); US 5,866,619 and US 6,368,629 (saccharide containing polymer); US 6,531,152 (describes a drug delivery system containing a water soluble core (Ca pectinate or other water-insoluble polymers) and outer coat which bursts (e.g. hydrophobic polymer-Eudragrit)); US 6,234,464; US 6,403,130 (coating with polymer containing casein and high methoxy pectin; WO0174 175 (Maillard reaction product); WO05063206 (solubility increasing formulation); WO040 19872 (transferring fusion proteins).

[60] The GCC peptides described herein may be formulated using gastrointestinal retention system technology (GIRES; Merrion Pharmaceuticals). GIRES comprises a controlled-release dosage form inside an inflatable pouch, which is placed in a drug capsule for oral administration. The capsule shell can be a HPMC capsule shell or Gelatin capsule shell. Upon dissolution of the capsule, a gas-generating system inflates the pouch in the stomach where it is retained for 16-24 hours, all the time releasing agents described herein.

[61] The GCC peptides described herein can also be formulated using the multi matrix system technology (MMX).

[62] The GCC peptides described herein can be formulated in an osmotic device including the ones disclosed in US 4,503,030, US 5,609,590 and US 5,358,502. US 4,503,030 discloses an osmotic device for dispensing a drug to certain pH regions of the gastrointestinal tract. More particularly, the invention relates to an osmotic device comprising a wall formed of a

semi-permeable pH sensitive composition that surrounds a compartment containing a drug, with a passageway through the wall connecting the exterior of the device with the compartment. The device delivers the drug at a controlled rate in the region of the gastrointestinal tract having a pH of less than 3.5, and the device self- destructs and releases all its drug in the region of the gastrointestinal tract having a pH greater than 3.5, thereby providing total availability for drug absorption. U.S. Patent Nos. 5,609,590 and 5, 358,502 disclose an osmotic bursting device for dispensing a beneficial agent to an aqueous environment. The device comprises a beneficial agent and osmagent surrounded at least in part by a semi-permeable membrane. The beneficial agent may also function as the osmagent. The semi-permeable membrane is permeable to water and substantially impermeable to the beneficial agent and osmagent. A trigger means is attached to the semi-permeable membrane (e.g., joins two capsule halves). The trigger means is activated by a pH of from 3 to 9 and triggers the eventual, but sudden, delivery of the beneficial agent. These devices enable the pH-triggered release of the beneficial agent core as a bolus by osmotic bursting.

[63] In one embodiment the formulation contains a GCC agonist peptide, mannitol, silicified microcrystalline cellulose, sodicum starch glycolate, and sodium stearyl fumarate. The GCC agonist is at a concentration of less than 5% w/w, less than 4%, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.23% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The mannitol is at a concentration of at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w, or at least 80% w/w. In some embodiments the mannitol is present at about 79% w/w (e.g., 79.77%). The mannitol is preferably Mannogem EZ. The silicified microcrystalline cellulose is at a concentration of at least 5% w/w, at least 10% w/w, or at least 15% w/w. In some embodiments the concentration of the silicified microcrystalline cellulose is about 15% w/w. The silicified microcrystalline cellulose is preferably Prosolv SMCC 90 LM. The sodicum starch glycolate is at a concentration of at least 1% w/w, at least 2% w/w, at least 3% w/w, or at least 4% w/w. In some embodiments the concentration of the sodicum starch glycolate is about 4% w/w. The sodicum starch glycolate is preferably Explotab. The sodium stearyl fumarate is at a concentration of at least 0.2% w/w, at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9, or at least 1% w/w. In some embodiments the concentration of the sodium stearyl fumarate is about 1% w/w. The sodium stearyl fumarate is preferably Pruv.

[64] In one embodiment the formulation contains a GCC agonist peptide, silicified microcrystalline cellulose, and sodicum starch glycolate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.3% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The silicified microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, or at least 95% w/w. In some embodiments the concentration of the silicified microcrystalline cellulose is about 95.7% w/w. The silicified microcrystalline cellulose is preferably Prosolv SMCC 90 HD. The sodicum starch glycolate is at a concentration of at least 1% w/w, at least 2% w/w, at least 3% w/w, or at least 4% w/w. In some embodiments the concentration of the sodicum starch glycolate is 4% w/w. The sodicum starch glycolate is preferably Explotab.

[65] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, calcium chloride dihydrate, leucine, and hyrpomellose. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.3246% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 99.10% w/w. The microcrystalline cellulose is preferably Celphere SCP-100. The calcium chloride dihydrate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the calcium chloride dihydrate is about 0.2622% w/w. The leucine is at a concentration of at least 0.05% w/w, at least 0.1% w/w, at least 0.12% w/w, or at least 0.15% w/w. In some embodiments the concentration of leucine is about 0.12% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the hypromellose is about 0.2% w/w. The hypromellose is preferably Methocel E5 PremLV.

[66] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, calcium chloride dihydrate, leucine, hypromellose, and magnesium stearate. The

GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.36% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 98.75% w/w. The microcrystalline cellulose is preferably Avicel PH 102. The calcium chloride dihydrate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, at least 0.25% w/w, or at least 0.3% w/w. In some embodiments the concentration of the calcium chloride dihydrate is about 0.29% w/w. The leucine is at a concentration of at least 0.05% w/w, at least 0.1% w/w, at least 0.12% w/w, or at least 0.15% w/w. In some embodiments the concentration of leucine is about 0.13% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the hypromellose is about 0.22% w/w. The hypromellose is preferably Methocel E5 PremLV. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[67] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.32% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 99.43% w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[68] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5%

w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.32% w/w, about 1.18% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 98.57 % w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[69] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.18% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 97.09 % w/w. The microcrystalline cellulose is preferably Avicel PH 112. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[70] In one embodiment the formulation contains a GCC agonist peptide, trehalose granules, hypromellose, histidine, calcium ascorbate, trehalose powder, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.18% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The trehalose granules are at a concentration of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, or at least 75% w/w. In some embodiments the concentration of the trehalose granules is 55-75% w/w. In a particular embodiment, the concentration of the trehalose granules is 70.48% w/w. The hypromellose is

at a concentration of at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4% w/w, or at least 0.5% w/w. In some embodiments the concentration of the hypromellose is 0.2-2% w/w. In a particular embodiment the concentration of the hypromellose about 0.5% w/w. The hypromellose is preferably Methocel ES Premium LV. The histine is a concentration of at least 0.6% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, at least 3% w/w, or at least 5% w/w. In some embodiments the concentration of the histidine is 1-6% w/w. In a particular embodiment, the concentration of the arginine is 1.48% w/w. The calcium ascorbate is at a concentration of at least 0.05% w/w, at least 0.07% w/w, at least 0.09% w/w, or at least 0.1% w/w. In some embodiments the concentration of the calcium ascorbate is 0.05-10% w/w. In a particular embodiment, the concentration of the calcium ascorbate is about 0.1% w/w. The trehalose powder is at a concentration of at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, or at least 1.2% w/w. In some embodiments the concentration of the trehalose powder is 0.5-4% w/w. In a particular embodiment, the concentration of the trehalose powder is 1.02% w/w. The microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, or at least 25% w/w. In some embodiments the concentration of the microcrystalline cellulose is 20-40% w/w. In a particular embodiment, the concentration of the microcrystalline cellulose is 25% w/w. The microcrystalline cellulose is preferably Avicel PH 200. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is 0.2-1% w/w. In a particular embodiment the concentration of the magnesium stearate is about 0.25% w/w.

[71] In one embodiment the formulation contains a GCC agonist peptide, trehalose granules, hypromellose, arginine, calcium ascorbate, trehalose powder, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.17% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The trehalose granules are at a concentration of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, or at least 75% w/w. In some embodiments the concentration of the trehalose granules is 55-75% w/w. In a particular embodiment, the concentration of the trehalose granules is 70.31% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4%

w/w, or at least 0.5% w/w. In some embodiments the concentration of the hypromellose is 0.2-2% w/w. In a particular embodiment the concentration of the hypromellose about 0.5% w/w. The hypromellose is preferably Methocel ES Premium LV. The arginine is a concentration of at least 0.5% w/w, at least 1% w/w, at least 1.5% w/w, or at least 2% w/w. In some embodiments the concentration of the arginine is 1-6% w/w. In a particular embodiment, the concentration of the arginine is 1.66% w/w. The calcium ascorbate is at a concentration of at least 0.05% w/w, at least 0.07% w/w, at least 0.09% w/w, or at least 0.1% w/w. In some embodiments the concentration of the calcium ascorbate is 0.05-10% w/w. In a particular embodiment, the concentration of the calcium ascorbate is about 0.1% w/w. The trehalose powder is at a concentration of at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, or at least 1.2% w/w. In some embodiments the concentration of the trehalose powder is 0.5-4% w/w. In a particular embodiment, the concentration of the trehalose powder is 1.02% w/w. The microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, or at least 25% w/w. In some embodiments the concentration of the microcrystalline cellulose is 20-40% w/w. In a particular embodiment, the concentration of the microcrystalline cellulose is 25% w/w. The microcrystalline cellulose is preferably Avicel PH 200. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is 0.2-1% w/w. In a particular embodiment the concentration of the magnesium stearate is about 0.25% w/w.

[72] In one embodiment the formulation contains a GCC agonist peptide, trehalose granules, hypromellose, TRIS, calcium ascorbate, trehalose powder, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.17% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The trehalose granules are at a concentration of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, or at least 75% w/w. In some embodiments the concentration of the trehalose granules is 55-75% w/w. In a particular embodiment, the concentration of the trehalose granules is 70.81% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4% w/w, or at least 0.5% w/w. In some embodiments the concentration of the hypromellose is 0.2-2% w/w. In a particular embodiment the concentration of the hypromellose about 0.5%

w/w. The hypromellose is preferably Methocel ES Premium LV. The TRIS is a concentration of at least 0.6% w/w, at least 0.8% w/w, at least 0.9% w/w, or at least 1% w/w. In some embodiments the concentration of the TRIS is 0.5-6% w/w. In a particular embodiment, the concentration of the arginine is 1.15% w/w. The calcium ascorbate is at a concentration of at least 0.05% w/w, at least 0.07% w/w, at least 0.1% w/w, or at least 1% w/w. In some embodiments the concentration of the calcium ascorbate is 0.05-10% w/w. In a particular embodiment, the concentration of the calcium ascorbate is about 0.1% w/w. The trehalose powder is at a concentration of at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, or at least 1.2% w/w. In some embodiments the concentration of the trehalose powder is 0.5-4% w/w. In a particular embodiment, the concentration of the trehalose powder is 1.02% w/w. The microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, or at least 25% w/w. In some embodiments the concentration of the microcrystalline cellulose is 20-40% w/w. In a particular embodiment, the concentration of the microcrystalline cellulose is 25% w/w. The microcrystalline cellulose is preferably Avicel PH 200. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is 0.2-1% w/w. In a particular embodiment the concentration of the magnesium stearate is about 0.25% w/w.

[73] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.10% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 98.64 % w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[74] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5%

w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 3.32% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 96.43 % w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

1.2 **GCC** Agonists

[75] The GCC agonists for use in the formulations and methods of the invention bind to guanylate cyclase C and stimulate intracellular production of cGMP. Optionally, the GCC agonists induce apoptosis and inhibit proliferation of epithelial cells. The term, "guanylate cyclase C" refers to a transmembrane form of guanylate cyclase that acts as the intestinal receptor for the heat-stable toxin (ST) peptides secreted by enteric bacteria. Guanylate cyclase C is also the receptor for the naturally occurring peptides guanylin and uroguanylin. The possibility that there may be different receptors for each of these peptides has not been excluded. Hence, the term "guanylate cyclase C" may also encompass a class of transmembrane guanylate cyclase receptors expressed on epithelial cells lining the gastrointestinal mucosa.

[76] The term "GCC agonist" refers to both peptides and non-peptide compounds such as that bind to an intestinal guanylate cyclase C and stimulate the intracellular production of cGMP. Where the GCC agonist is a peptide, the term encompasses biologically active fragments of such peptides and pro-peptides that bind to guanylate cyclase C and stimulate the intracellular production of cGMP.

[77] Preferably, the GCC agonists for use in the formulations and methods of the invention stimulate intracellular cGMP production at higher levels than naturally occurring GCC agonists such as uroguanylin, guanylin, and ST peptides. In some embodiments, the GCC agonists stimulate intracellular cGMP production at higher levels than the peptide designated

SP-304 (SEQ ID NO:1). In specific embodiments, a GCC agonist for use in the formulations and methods of the invention stimulates 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared to uroguanylin, guanylin, lymphoguanylin, linaclotide, ST peptides, or SP-304. The terms "induce" and "stimulate"are used interchangeably throughout the specification.

[78] Preferably, the GCC agonists for use in the formulations and methods of the invention are more stable than naturally occurring GCC agonists such as uroguanylin, guanylin, and ST peptides. In some embodiments, the GCC agonists are more stable than the peptide designated SP-304. "Stability" in this context refers to resistance to degradation in gastrointestinal fluid and/or intestinal fluid (or simulated gastrointestinal or intestinal fluids) compared to the reference peptide. For example, the GCC agonists for use in the formulations and methods of the invention preferably degrade 2%, 3%, 5%, 10%, 15%, 20%, 30%, 40%, 50% , 75%, 90% or less compared to naturally occurring GCC angonists and/or SP-304.

[79] The GCC agonists for use in the formulations and methods of the invention are preferably peptides. In some embodiments, the GCC agonist peptide is less than 30 amino acids in length. In particular embodiments, the GCC agonist peptide is less than or equal to 30, 25, 20, 15, 14, 13, 12, 11, 10, or 5 amino acids in length. Examples of GCC agonist peptides for use in the formulations and methods of the invention include those described in U.S. Serial Nos.: 12/133,344, filed June 4, 2008, 12/478505, filed June 4, 2009; 12/478511, filed June 4, 2009; 12/504288, filed July 16, 2009; and U.S. Provisional Application Serial Nos.: 60/933194, filed June 4, 2007; 61/058,888, filed June 4, 2008; 61/058,892, filed June 4, 2008; and 61/081,289, filed July 16, 2008, each of which is incorporated by reference herein in its entirety.

[80] Specific examples of GCC agonist peptides for use in the formulations and methods of the invention include those described in Tables I-VII below. As used Tables I-VII, the terms "PEG3" or "3PEG" refer to a polyethylene glycol such as aminoethyloxy-ethyloxy-acetic acid (AeeA), and polymers thereof. The term "X_{aa}" refers to any natural or unnatural amino acid or amino acid analogue. The term "M_{aa}" refers to a cysteine (Cys), penicillamine (Pen) homocysteine, or 3-mercaptoproline. The term "Xaa_{n1}" is meant to denote an amino acid sequence of any natural or unnatural amino acid or amino acid analogue that is one, two

or three residues in length; Xaa_{n2} is meant to denote an amino acid sequence that is zero or one residue in length; and Xaa_{n3} is meant to denote an amino acid sequence zero, one, two, three, four , five or six residues in length. Additionally, any amino acid represented by Xaa, Xaa_{n1}, Xaa_{n2}, or Xaa_{n3} may be an L-amino acid, a D-amino acid, a methylated amino acid or any combination of thereof. Optionally, any GCC agonist peptide represented by Formulas I to XX in the tables may contain on or more polyethylene glycol residues at the the N-terminus, C-terminus or both.

[81] In certain embodiments, a GCC agonist formulation of the invention comprises a peptide selected from SEQ ID NOs: 1-249, the sequences of which are set forth below in Tables I to VII below. In one embodiment, a GCC agonist formulation comprises the peptide designated by SEQ ID NOs:1, 8, 9, 55, or 56.

[82] In certain embodiments, a GCC agonist formulation of the invention comprises a peptide that is substantially equivalent to a peptide selected from SEQ ID NOs: 1-249. The term "substantially equivalent" refers to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without impairing the peptide's ability to bind to an intestinal guanylate cyclase receptor and stimulate fluid and electrolyte transport.

1.2.1 GCC Agonist Peptides

[83] In a preferred embodiment, the GCC agonists for use in the formulations and methods of the invention are GCC agonist peptides. In certain embodiments, the GCC agonist peptides are analogues of uroguanylin or a bacterial ST peptide. Uroguanylin is a circulating peptide hormone with natriuretic activity. An ST peptide is a member of a family of heat stable enterotoxins (ST peptides) secreted by pathogenic strains of *E. coli* and other enteric bacteria that activate guanylate cyclase receptor and cause secretory diarrhea. Unlike bacterial ST peptides, the binding of uroguanylin to guanylate cyclase receptor is dependent on the physiological pH of the gut. Therefore, uroguanylin is expected to regulate fluid and electrolyte transport in a pH dependent manner and without causing severe diarrhea.

[84] The GCC agonist peptides for use in the formulations and methods of the invention can be polymers of L-amino acids, D-amino acids, or a combination of both. For example, in various embodiments, the peptides are D retro-inverso peptides. The term "retro-inverso

isomer" refers to an isomer of a linear peptide in which the direction of the sequence is reversed and the chirality of each amino acid residue is inverted. *See*, *e.g.*, Jameson *et al.*, *Nature*, 368, 744-746 (1994); Brady *et al.*, Nature, 368, 692-693 (1994). The net result of combining D-enantiomers and reverse synthesis is that the positions of carbonyl and amino groups in each amide bond are exchanged, while the position of the side-chain groups at each alpha carbon is preserved. Unless specifically stated otherwise, it is presumed that any given L-amino acid sequence of the invention may be made into a D retro-inverso peptide by synthesizing a reverse of the sequence for the corresponding native L-amino acid sequence.

[85] The GCC agonist peptides for use in the formulations and methods of the invention are able to induce intracellular cGMP production in cells and tissues expressing guanylate cyclase C. In certain embodiments, the GCC agonist peptide stimulates 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared to naturally occurring GCC agonists such as uroguanylin, guanylin, or ST peptides. Optionally, the GCC agonist peptide stimulates 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared SP-304 (SEQ ID NO:1). In further embodiments, the GCC agonist peptide stimulates apoptosis, *e.g.*, programmed cell death, or activate the cystic fibrosis transmembrane conductance regulator (CFTR).

[86] In some embodiments, the GCC agonist peptides for use in the formulations and methods of the invention are more stable than naturally occurring GCC agonists and/or SP-304 (SEQ ID NO:1), SP-339 (linaclotide) (SEQ ID NO: 55) or SP-340 (SEQ ID NO: 56). For example, the GCC agonist peptide degrades 2%, 3%, 5%, 10%, 15%, 20%, 30%, 40%, 50% , 75%, 90% or less compared to naturally occurring GCC agonists and/or SP-304, SP-339 (linaclotide) or SP-340. In certain embodiments, the GCC agonist peptides for use in the formulations and methods of the invention are more stable to proteolytic digestion than naturally occurring GCC agonists and/or SP-304 (SEQ ID NO:1), SP-339 (linaclotide) (SEQ ID NO: 55) or SP-340 (SEQ ID NO: 56). In one embodiment, a GCC agonist peptide is pegylated in order to render the peptides more resistant towards protealysis by enzymes of the gastrointestinal tract. In a preferred embodiment, the GCC agonist peptide is pegylated with the aminoethyloxy-ethyloxy-acetic acid (Aeea) group at its C-terminal end, at its N-terminal end, or at both termini.

[87] Specific examples of GCC agonist peptides that can be used in the methods and formulations of the invention include a peptide selected from the group designated by SEQ ID NOs: 1-249.

[88] In one embodiment, the GCC agonist peptide is a peptide having the amino acid sequence of any one of Formulas X- XVII (*e.g.* SEQ ID NO:87-98).

[89] In some embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula I, wherein at least one amino acid of Formula I is a D-amino acid or a methylated amino acid and/or the amino acid at position 16 is a serine. Preferably, the amino acid at position 16 of Formula I is a D-amino acid or a methylated amino acid. For example, the amino acid at position 16 of Formula I is a d-leucine or a d-serine. Optionally, one or more of the amino acids at positions 1-3 of Formula I are D-amino acids or methylated amino acids or a combination of D-amino acids or methylated amino acids. For example, Asn^1, Asp^2 or Glu^3 (or a combination thereof) of Formula I is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula I is a leucine, serine or tyrosine.

[90] In alternative embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula II, wherein at least one amino acid of Formula II is a D-amino acid or a methylated amino acid. Preferably, the amino acid denoted by Xaa_{n2} of Formula II is a D-amino acid or a methylated amino acid. In some embodiments, the amino acid denoted by Xaa_{n2} of Formula II is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more amino acids denoted by Xaa_{n1} of Formula II is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula II is a leucine, a serine, or a tyrosine.

[91] In some embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula III, wherein at least one amino acid of Formula III is a D-amino acid or a methylated amino acid and/or Maa is not a cysteine. Preferably, the amino acid denoted by Xaa_{n2} of Formula III is a D-amino acid or a methylated amino acid. In some embodiments the amino acid denoted by Xaa_{n2} of Formula III is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more amino acids denoted by Xaa_{n1} of Formula III is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula III is a leucine, a serine, or a tyrosine.

[92] In other embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula IV, wherein at least one amino acid of Formula IV is a D-amino acid or a methylated amino acid, and/or Maa is not a cysteine. Preferably, the Xaa_{n2} of Formula IV is a D-amino acid or a methylated amino acid. In some embodiments, the amino acid denoted by Xaa_{n2} of Formula IV is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more of the amino acids denoted by Xaa_{n1} of Formula IV is a D-amino acid or a methylated amino acid. Preferably, the amino acid denoted Xaa^6 of Formula IV is a leucine, a serine, or a tyrosine.

[93] In further embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula V, wherein at at least one amino acid of Formula V is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position 16 of Formula V is a D-amino acid or a methylated amino acid. For example, the amino acid at position 16 (i.e., Xaa^{16}) of Formula V is a d-leucine or a d-serine. Optionally, one or more of the amino acids at position 1-3 of Formula V are D-amino acids or methylated amino acids or a combination of D-amino acids or methylated amino acids. For example, Asn^1, Asp^2 or Glu^3 (or a combination thereof) of Formula V is a D-amino acids or a methylated amino acid. Preferably, the amino acid denoted at Xaa^6 of Formula V is a leucine, a serine, or a tyrosine.

[94] In additional embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula VI, VII, VIII, or IX. Preferably, the amino acid at position 6 of Formula VI, VII, VIII, or IX is a leucine, a serine, or a tyrosine. In some aspects the amino acid at position 16 of Formula VI, VII, VIII, or IX is a leucine or a serine. Preferably, the amino acid at position 16 of Formula V is a D-amino acid or a methylated amino acid.

[95] In additional embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula X, XI, XII, XIII, XIV, XV, XVI or XVII. Optionally, one or more amino acids of Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-amino acid or a methylated amino acid. Preferably, the amino acid at the carboxy terminus of the peptides according to Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-amino acid or a methylated amino acid. For example the the amino acid at the carboxy terminus of the peptides according to Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-tyrosine.

[96] Preferably, the amino acid denoted by Xaa^6 of Formula XIV is a tyrosine, phenyalanine or a serine. Most preferably the amino acid denoted by Xaa^6 of Formula XIV is

a phenyalanine or a serine. Preferably, the amino acid denoted by Xaa^4 of Formula XV, XVI or XVII is a tyrosine, a phenyalanine, or a serine. Most preferably, the amino acid position Xaa^4 of Formula V, XVI or XVII is a phenyalanine or a serine.

[97] In some embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula XVIII. Preferably, the amino acid at position 1 of Formula XVIII is a glutamic acid, aspartic acid, glutamine or lysine. Preferably, the amino acid at position 2 and 3 of Formula XVIII is a glutamic acid, or an aspartic acid. Preferably, the amino acid at position 5 a glutamic acid. Preferably, the amino acid at position 6 of Formula XVIII is an isoleucine, valine, serine, threonine or tyrosine. Preferably, the amino acid at position 8 of Formula XVIII is a valine or isoleucine. Preferably, the amino acid at position 9 of Formula XVIII is a an asparagine. Preferably, the amino acid at position 10 of Formula XVIII is a valine or an methionine. Preferably, the amino acid at position 11 of Formula XVIII is an alanine. Preferably, the amino acid at position 13 of Formula XVIII is a threonine. Preferably, the amino acid at position 14 of Formula XVIII is a glycine. Preferably, the amino acid at position 16 of Formula XVIII is a leucine, serine or threonine

[98] In alternative embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula XIX. Preferably, the amino acid at position 1 of Formula XIX is a serine or asparagine. Preferably, the amino acid at position 2 of Formula XIX is a histidine or an aspartic acid. Preferably, the amino acid at position 3 of Formula XIX is a threonine or a glutamic acid. Preferably, the amino acid at position 5 of Formula XIX is a glutamic acid. Preferably, the amino acid at position 6 of Formula XIX is an isoleucine, leucine, valine or tyrosine. Preferably, the amino acid at position 8, 10, 11, or 13 of Formula XIX is a alanine. Preferably, the amino acid at position 9 of Formula XIX is an asparagine or a phenylalanine. Preferably, the amino acid at position 14 of Formula XIX is a glycine.

[99] In further embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula XX. Preferably, the amino acid at position 1 of Formula XX is a glutamine. Preferably, the amino acid at position 2 or 3 of Formula XX is a glutamic acid or a aspartic acid. Preferably, the amino acid at position 5 of Formula XX is a glutamic acid. Preferably, the amino acid at position 6 of Formula XX is threonine, glutamine, tyrosine, isoleucine, or leucine. Preferably, the amino acid at position 8 of Formula XX is isoleucine or valine. Preferably, the amino acid at position 9 of Formula XX is asparagine. Preferably,

the amino acid at position 10 of Formula XX is methionine or valine. Preferably, the amino acid at position 11 of Formula XX is alanine. Preferably, the amino acid at position 13 of Formula XX is a threonione. Preferably, the amino acid at position 1 of Formula XX is a glycine. Preferably, the amino acid at position 15 of Formula XX is a tyrosine. Optionally, the amino acid at position 15 of Formula XX is two amino acid in length and is Cysteine (Cys), Penicillamine (Pen) homocysteine, or 3-mercaptoproline and serine, leucine or threonine.

[100] In certain embodiments, one or more amino acids of the GCC agonist peptides are replaced by a non-naturally occurring amino acid or a naturally or non-naturally occurring amino acid analog. Such amino acids and amino acid analogs are known in the art. See, for example, Hunt, "The Non-Protein Amino Acids," in *Chemistry and Biochemistry of the Amino Acids*, Barrett, Chapman and Hall, 1985. In some embodiments, an amino acid is replaced by a naturally-occurring, non-essential amino acid, *e.g.*, taurine. Non-limiting examples of naturally occurring amino acids that can be replaced by non-protein amino acids include the following: (1) an aromatic amino acid can be replaced by 3,4-dihydroxy-L-phenylalanine, 3-iodo-L-tyrosine, triiodothyronine, L-thyroxine, phenylglycine (Phg) or nor-tyrosine (norTyr); (2) Phg and norTyr and other amino acids including Phe and Tyr can be substituted by, *e.g.*, a halogen, -CH3, -OH, -CH2NH3, -C(O)H, -CH2CH3, - CN, -CH2CH2CH3, -SH, or another group; (3) glutamine residues can be substituted with gamma-Hydroxy-Glu or gamma- Carboxy-Glu; (4) tyrosine residues can be substituted with an alpha substituted amino acid such as L-alpha-methylphenylalanine or by analogues such as: 3-Amino-Tyr; Tyr(CH3); Tyr(PO3(CH3)2); Tyr(SO3H); beta-Cyclohexyl-Ala; beta-(l-Cyclopentenyl)-Ala; beta- Cyclopentyl-Ala; beta-Cyclopropyl-Ala; beta-Quinolyl-Ala; beta-(2-Thiazolyl)-Ala; beta- (Triazole-l-yl)-Ala; beta-(2-Pyridyl)-Ala; beta-(3-Pyridyl)-Ala; Amino-Phe; Fluoro-Phe; Cyclohexyl-Gly; tBu-Gly; beta-(3-benzothienyl)-Ala; beta-(2-thienyl)-Ala; 5-Methyl-Trp; and A- Methyl-Trp; (5) proline residues can be substituted with homopro (L-pipecolic acid); hydroxy-Pro; 3,4-Dehydro-Pro; 4-fluoro-Pro; or alpha-methyl-Pro or an N(alpha)-C(alpha) cyclized amino acid analogues with the structure: n = 0, 1, 2, 3; and (6) alanine residues can be substituted with alpha-substitued or N-methylated amino acid such as alpha-amino isobutyric acid (aib), L/D-alpha-ethylalanine (L/D-isovaline), L/D-methylvaline, or L/D-alpha-methylleucine or a non-natural amino acid such as beta-fluoro-Ala. Alanine can also be substituted with: n = 0, 1, 2, 3 Glycine residues can be substituted with alpha-amino isobutyric acid (aib) or L/D-alpha- ethylalanine (L/D-isovaline).

[101] Further examples of non-natural amino acids include: an unnatural analog of tyrosine; an unnatural analogue of glutamine; an unnatural analogue of phenylalanine; an unnatural analogue of serine; an unnatural analogue of threonine; an alkyl, aryl, acyl, azido, cyano, halo, hydrazine, hydrazide, hydroxyl, alkenyl, alkynl, ether, thiol, sulfonyl, seleno, ester, thioacid, borate, boronate, phospho, phosphono, phosphine, heterocyclic, enone, imine, aldehyde, hydroxylamine, keto, or amino substituted amino acid, or any combination thereof; an amino acid with a photoactivatable cross-linker; a spin-labeled amino acid; a fluorescent amino acid; an amino acid with a novel functional group; an amino acid that covalently or noncovalently interacts with another molecule; a metal binding amino acid; an amino acid that is amidated at a site that is not naturally amidated, a metal-containing amino acid; a radioactive amino acid; a photocaged and/or photoisomerizable amino acid; a biotin or biotin-analogue containing amino acid; a glycosylated or carbohydrate modified amino acid; a keto containing amino acid; amino acids comprising polyethylene glycol or polyether; a heavy atom substituted amino acid (*e.g.*, an amino acid containing deuterium, tritium, ^{13}C, ^{15}N, or ^{18}O); a chemically cleavable or photocleavable amino acid; an amino acid with an elongated side chain; an amino acid containing a toxic group; a sugar substituted amino acid, *e.g.*, a sugar substituted serine or the like; a carbon-linked sugar-containing amino acid; a redox-active amino acid; an α-hydroxy containing acid; an amino thio acid containing amino acid; an α, α disubstituted amino acid; a β- amino acid; a cyclic amino acid other than proline; an O-methyl-L-tyrosine; an L-3-(2- naphthyl)alanine; a 3-methyl-phenylalanine; a ρ-acetyl-L-phenylalanine; an O-4-allyl-L-tyrosine; a 4-propyl-L-tyrosine; a tri-O-acetyl-GlcNAc β - serine; an L-Dopa; a fluorinated phenylalanine; an isopropyl-L-phenylalanine; a p-azido-L-phenylalanine; a p-acyl-L-phenylalanine; a p- benzoyl-L-phenylalanine; an L-phosphoserine; a phosphonoserine; a phosphonotyrosine; a p- iodo-phenylalanine; a 4-fluorophenylglycine; a p-bromophenylalanine; a p-amino-L- phenylalanine; an isopropyl-L-phenylalanine; L-3-(2-naphthyl)alanine; D- 3-(2-naphthyl)alanine (dNal); an amino-, isopropyl-, or O-allyl-containing phenylalanine analogue; a dopa, 0-methyl-L-tyrosine; a glycosylated amino acid; a p-(propargyloxy)phenylalanine; dimethyl-Lysine; hydroxy-proline; mercaptopropionic acid; methyl-lysine; 3-nitro-tyrosine; norleucine; pyro-glutamic acid; Z (Carbobenzoxyl); ε-Acetyl-Lysine; β-alanine; aminobenzoyl derivative; aminobutyric acid (Abu); citrulline; aminohexanoic acid; aminoisobutyric acid (AIB); cyclohexylalanine; d-cyclohexylalanine; hydroxyproline; nitro-arginine; nitro-phenylalanine; nitro-tyrosine; norvaline; octahydroindole carboxylate; ornithine (Orn); penicillamine (PEN); tetrahydroisoquinoline;

acetamidomethyl protected amino acids and pegylated amino acids. Further examples of unnatural amino acids and amino acid analogs can be found in U.S. 20030108885, U.S. 20030082575, US20060019347 (paragraphs 410-418) and the references cited therein. The polypeptides of the invention can include further modifications including those described in US20060019347, paragraph 589. Exempary GCC agonist peptides which include a non-naturally occurring amino acid include for example SP-368 and SP-369.

[102] In some embodiments, the GCC agonist peptides are cyclic peptides. GCC agonist cyclic peptides can be prepared by methods known in the art. For example, macrocyclization is often accomplished by forming an amide bond between the peptide N- and C-termini, between a side chain and the N- or C-terminus [*e.g.*, with $K_3Fe(CN)_6$ at pH 8.5] (Samson *et al.*, *Endocrinology,* 137: 5182-5185 (1996)), or between two amino acid side chains, such as cysteine. See, *e.g.,* DeGrado, *Adv Protein Chem, 39*: 51-124 (1988). In various embodiments, the GCC agonist peptides are [4,12; 7,15] bicycles.

[103] In certain embodiments, one or both Cys residues which normally form a disulfide bond in a GCC agonist peptide are replaced with homocysteine, penicillamine, 3-mercaptoproline (Kolodziej *et al.* 1996 *Int. J. Pept. Protein Res.* 48:274), β, β dimethylcysteine (Hunt *et al.* 1993 *Int. J. Pept. Protein Res.* 42:249), or diaminopropionic acid (Smith *et al.* 1978 *J. Med. Chem.* 2 1:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

[104] In certain embodiments, one or more disulfide bonds in a GCC agonist peptide are replaced by alternative covalent cross-links, *e.g.*, an amide linkage ($-CH_2CH(O)NHCH_2-$ or $-CH_2NHCH(O)CH_2-$), an ester linkage, a thioester linkage, a lactam bridge, a carbamoyl linkage, a urea linkage, a thiourea linkage, a phosphonate ester linkage, an alkyl linkage ($-CH_2CH_2CH_2CH_2-$), an alkenyl linkage ($-CH_2CH=CHCH_2-$), an ether linkage ($-CH_2CH_2OCH_2-$ or $-CH_2OCH_2CH_2-$), a thioether linkage ($-CH_2CH_2SCH_2-$ or $-CH_2SCH_2CH_2-$), an amine linkage ($-CH_2CH_2NHCH_2-$ or $-CH_2NHCH_2CH_2-$) or a thioamide linkage ($-CH_2CH(S)HNHCH_2-$ or $-CH_2NHCH(S)CH_2-$). For example, Ledu *et al.* (*Proc. Natl. Acad. Sci.* 100:11263-78, 2003) describe methods for preparing lactam and amide cross-links. Exemplary GCC agonist peptides which include a lactam bridge include, for example, SP-370.

[105] In certain embodiments, the GCC agonist peptides have one or more conventional polypeptide bonds replaced by an alternative bond. Such replacements can increase the stability of the polypeptide. For example, replacement of the polypeptide bond between a residue amino terminal to an aromatic residue (*e.g.* Tyr, Phe, Trp) with an alternative bond can reduce cleavage by carboxy peptidases and may increase half-life in the digestive tract. Bonds that can replace polypeptide bonds include: a retro-inverso bond (C(O)-NH instead of NH-C(O); a reduced amide bond (NH-CH_2); a thiomethylene bond (S-CH_2 or CH_2-S); an oxomethylene bond (O-CH_2 or CH_2-O); an ethylene bond (CH_2-CH_2); a thioamide bond (C(S)-NH); a trans-olefine bond (CH=CH); a fiuoro substituted trans-olefme bond (CF=CH); a ketomethylene bond (C(O)-CHR or CHR-C(O) wherein R is H or CH_3; and a fluoro-ketomethylene bond (C(O)-CFR or CFR-C(O) wherein R is H or F or CH_3.

[106] In certain embodiments, the GCC agonist peptides are modified using standard modifications. Modifications may occur at the amino (N-), carboxy (C-) terminus, internally or a combination of any of the preceeding. In one aspect described herein, there may be more than one type of modification on the polypeptide. Modifications include but are not limited to: acetylation, amidation, biotinylation, cinnamoylation, farnesylation, formylation, myristoylation, palmitoylation, phosphorylation (Ser, Tyr or Thr), stearoylation, succinylation, sulfurylation and cyclisation (via disulfide bridges or amide cyclisation), and modification by Cys3 or Cys5. The GCC agonist peptides described herein may also be modified by 2, 4-dinitrophenyl (DNP), DNP-lysine, modification by 7-Amino-4-methyl-coumarin (AMC), flourescein, NBD (7-Nitrobenz-2-Oxa-l,3-Diazole), p-nitro-anilide, rhodamine B, EDANS (5-((2-aminoethyl)amino)naphthalene-l- sulfonic acid), dabcyl, dabsyl, dansyl, texas red, FMOC, and Tamra (Tetramethylrhodamine). The GCC agonist peptides described herein may also be conjugated to, for example, polyethylene glycol (PEG); alkyl groups (e.g., C1-C20 straight or branched alkyl groups); fatty acid radicals; combinations of PEG, alkyl groups and fatty acid radicals (*See*, U.S. Patent 6,309,633; Soltero et al., 2001 Innovations in Pharmaceutical Technology 106-110); BSA and KLH (Keyhole Limpet Hemocyanin). The addition of PEG and other polymers which can be used to modify polypeptides of the invention is described in US20060 19347 section IX.

[107] A GCC agonist peptide can also be a derivatives of a GCC agonist peptide described herein. For example, a derivative includes hybrid and modified forms of GCC agonist peptides in which certain amino acids have been deleted or replaced. A modification may

also include glycosylation. Preferrably, where the modification is an amino acid substitution, it is a conservative substitution at one or more positions that are predicted to be non-essential amino acid residues for the biological activity of the peptide. A "conservative substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine).

[108] In one embodiment, a GCC agonist peptide described herein is subjected to random mutagenesis in order to identify mutants having biological activity.

[109] In one embodiment, the GCC agonist peptide is substantially homologous is a GCC agonist peptide described herein. Such substantially homologous peptides can be isolated by virtue of cross-reactivity with antibodies to a GCC agonist peptide described herein.

[110] Further examples of GCC agonist peptides that can be used in the methods and formulations of the invention are found in Tables I - VII below.

1.2.2 Preparation of GCC agonist peptides

[111] GCC agonist peptides can be prepared using art recognized techniques such as molecular cloning, peptide synthesis, or site-directed mutagenesis.

[112] Peptide synthesis can be performed using standard solution phase or solid phase peptide synthesis techniques or a combination of both process where segments are synthesized by solid phase and condensed in solution phase, in which a peptide linkage occurs through the direct condensation of the amino group of one amino acid with the carboxy group of the other amino acid with the elimination of a water molecule. Peptide bond synthesis by direct condensation, as formulated above, requires suppression of the reactive character of the amino group of the first and of the carboxyl group of the second

amino acid. The masking substituents must permit their ready removal, without inducing breakdown of the labile peptide molecule.

[113] In solution phase synthesis, a wide variety of coupling methods and protecting groups may be used (*See*, Gross and Meienhofer, eds., "The Peptides: Analysis, Synthesis, Biology," Vol. 1-4 (Academic Press, 1979); Bodansky and Bodansky, "The Practice of Peptide Synthesis," 2d ed. (Springer Verlag, 1994)). In addition, intermediate purification and linear scale up are possible. Those of ordinary skill in the art will appreciate that solution synthesis requires consideration of main chain and side chain protecting groups and activation method. In addition, careful segment selection is necessary to minimize racemization during segment condensation. Solubility considerations are also a factor. Solid phase peptide synthesis uses an insoluble polymer for support during organic synthesis. The polymer-supported peptide chain permits the use of simple washing and filtration steps instead of laborious purifications at intermediate steps. Solid-phase peptide synthesis may generally be performed according to the method of Merrifield et al., J. Am. Chem. Soc., 1963, 85:2149, which involves assembling a linear peptide chain on a resin support using protected amino acids. Solid phase peptide synthesis typically utilizes either the Boc or Fmoc strategy, which are well known in the art.

[114] Those of ordinary skill in the art will recognize that, in solid phase synthesis, deprotection and coupling reactions must go to completion and the side-chain blocking groups must be stable throughout the synthesis. In addition, solid phase synthesis is generally most suitable when peptides are to be made on a small scale.

[115] Acetylation of the N-terminal can be accomplished by reacting the final peptide with acetic anhydride before cleavage from the resin. C-amidation is accomplished using an appropriate resin such as methylbenzhydrylamine resin using the Boc technology.

[116] Alternatively the GCC agonist peptides are produced by modern cloning techniques For example, the GCC agonist peptides are produced either in bacteria including, without limitation, E. coli, or in other existing systems for polypeptide or protein production (*e.g.*, Bacillus subtilis, baculovirus expression systems using Drosophila Sf9 cells, yeast or filamentous fungal expression systems, mammalian cell expression systems), or they can be chemically synthesized. If the GCC agonist peptide or variant peptide is to be produced in bacteria, *e.g.*, E. coli, the nucleic acid molecule encoding the polypeptide may also encode a

leader sequence that permits the secretion of the mature polypeptide from the cell. Thus, the sequence encoding the polypeptide can include the pre sequence and the pro sequence of, for example, a naturally-occurring bacterial ST polypeptide. The secreted, mature polypeptide can be purified from the culture medium.

[117] The sequence encoding a GCC agonist peptide described herein can be inserted into a vector capable of delivering and maintaining the nucleic acid molecule in a bacterial cell. The DNA molecule may be inserted into an autonomously replicating vector (suitable vectors include, for example, pGEM3Z and pcDNA3, and derivatives thereof). The vector nucleic acid may be a bacterial or bacteriophage DNA such as bacteriophage lambda or M13 and derivatives thereof. Construction of a vector containing a nucleic acid described herein can be followed by transformation of a host cell such as a bacterium. Suitable bacterial hosts include but are not limited to, E. coli, B subtilis, Pseudomonas, Salmonella. The genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences.

[118] A variety of transcriptional control sequences are well known to those in the art. The expression vector can also include a translation regulatory sequence (*e.g.*, an untranslated 5' sequence, an untranslated 3' sequence, or an internal ribosome entry site). The vector can be capable of autonomous replication or it can integrate into host DNA to ensure stability during polypeptide production.

[119] The protein coding sequence that includes a GCC agonist peptide described herein can also be fused to a nucleic acid encoding a polypeptide affinity tag, *e.g.*, glutathione S-transferase (GST), maltose E binding protein, protein A, FLAG tag, hexa-histidine, myc tag or the influenza HA tag, in order to facilitate purification. The affinity tag or reporter fusion joins the reading frame of the polypeptide of interest to the reading frame of the gene encoding the affinity tag such that a translational fusion is generated. Expression of the fusion gene results in translation of a single polypeptide that includes both the polypeptide of interest and the affinity tag. In some instances where affinity tags are utilized, DNA sequence encoding a protease recognition site will be fused between the reading frames for the affinity tag and the polypeptide of interest.

[120] Genetic constructs and methods suitable for production of immature and mature forms of the GCC agonist peptides and variants described herein in protein expression systems other than bacteria, and well known to those skilled in the art, can also be used to produce polypeptides in a biological system.

[121] The peptides disclosed herein may be modified by attachment of a second molecule that confers a desired property upon the peptide, such as increased half-life in the body, for example, pegylation. Such modifications also fall within the scope of the term "variant" as used herein.

Table I. GCRA Peptides (SP-304 and Derivatives)

Name	Position of Disulfide bonds	Structure	SEQ ID NO
SP-304	C4:C12, C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	1
SP-326	C3:C11, C6:C14	Asp^{1}-Glu^{2}-Cys^{3}-Glu^{4}-Leu^{5}-Cys^{6}-Val^{7}-Asn^{8}-Val^{9}-Ala^{10}-Cys^{11}-Thr^{12}-Gly^{13}-Cys^{14}-Leu^{15}	2
SP-327	C2:C10, C5:C13	Asp^{1}-Glu^{2}-Cys^{3}-Glu^{4}-Leu^{5}-Cys^{6}-Val^{7}-Asn^{8}-Val^{9}-Ala^{10}-Cys^{11}-Thr^{12}-Gly^{13}-Cys^{14}	3
SP-328	C2:C10, C5:C13	Glu^{1}-Cys^{2}-Glu^{3}-Leu^{4}-Cys^{5}-Val^{6}-Asn^{7}-Val^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Leu^{14}	4
SP-329	C2:C10, C5:C13	Glu^{1}-Cys^{2}-Glu^{3}-Leu^{4}-Cys^{5}-Val^{6}-Asn^{7}-Val^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}	5
SP-330	C1:C9, C4:C12	Cys^{1}-Glu^{2}-Leu^{3}-Cys^{4}-Val^{5}-Asn^{6}-Val^{7}-Ala^{8}-Cys^{9}-Thr^{10}-Gly^{11}-Cys^{12}-Leu^{13}	6
SP-331	C1:C9, C4:C12	Cys^{1}-Glu^{2}-Leu^{3}-Cys^{4}-Val^{5}-Asn^{6}-Val^{7}-Ala^{8}-Cys^{9}-Thr^{10}-Gly^{11}-Cys^{12}	7
SP332	C4:C12,C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$	8
SP-333	C4:C12,C7:C15	$dAsn^{1}$-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$	9
SP-334	C4:C12,C7:C15	$dAsn^{1}$-$dAsp^{2}$-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$	10
SP-335	C4:C12,C7:C15	$dAsn^{1}$-$dAsp^{2}$-$dGlu^{3}$-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$	11
SP-336	C4:C12,C7:C15	$dAsn^{1}$-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	12
SP-337	C4:C12,C7:C15	$dAsn^{1}$-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-$dLeu^{6}$-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$	13
SP-338	C4:C12, C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}	14
SP-342	C4:C12, C7:C15	PEG3-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$-PEG3	15
SP-343	C4:C12, C7:C15	PEG3-$dAsn^{1}$-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$-PEG3	16
SP-344	C4:C12, C7:C15	PEG3-$dAsn^{1}$-$dAsp^{2}$-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$-PEG3	17
SP-347	C4:C12, C7:C15	$dAsn^{1}$-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$-PEG3	18
SP-348	C4:C12, C7:C15	PEG3-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$	19

SP-350	C4:C12, C7:C15	PEG3-dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	20
SP-352	C4:C12, C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}-PEG3	21
SP-358	C4:C12,C7:C15	PEG3-dAsn^{1}-dAsp^{2}-dGlu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}-PEG3	22
SP-359	C4:C12,C7:C15	PEG3-dAsn^{1}-dAsp^{2}-dGlu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	23
SP-360	C4:C12, C7:C15	dAsn^{1}-dAsp^{2}-dGlu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}-PEG3	24
SP-361	C4:C12, C7:C15	dAsn^{1}-dAsp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16} -PEG3	25
SP-362	C4:C12, C7:C15	PEG3-dAsn^{1}-dAsp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	26
SP-368	C4:C12, C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dNal^{16}	27
SP-369	C4:C12, C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-AIB^{8}-Asn^{9}-AIB^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	28
SP-370	C4:C12, C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Asp[Lactam]^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Orn^{15}-dLeu^{1}	29
SP-371	C4:C12,C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	30
SP-372	C4:C12,C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	31
N1	C4:C12,C7:C15	PEG3-dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16} -PEG3	32
N2	C4:C12,C7:C15	PEG3-dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	33
N3	C4:C12,C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16} PEG3	34
N4	C4:C12,C7:C15	PEG3-dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16} -PEG3	35
N5	C4:C12,C7:C15	PEG3-dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16}	36
N6	C4:C12,C7:C15	dAsn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dLeu^{16} -PEG3	37
N7	C4:C12,C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	38
N8	C4:C12,C7:C15	PEG3-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}-PEG3	39
N9	C4:C12,C7:C15	PEG3-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	40
N10	C4:C12,C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}-PEG3	41

N11	C4:C12,C7:C15	PEG3-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dSer^{16} -PEG3	42
N12	C4:C12,C7:C15	PEG3-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dSer^{16}	43
N13	C4:C12,C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dSer^{16} -PEG3	44
Formula I	C4:C12,C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-Xaa^{16}	45
Formula II	C4:C12,C7:C15	Xaa$_{n1}$-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-Xaa$_{n2}$^{16}	46
Formula III	4:12,7:15	Xaa$_{n1}$-Maa^{4}-Glu^{5}-Xaa^{6}-Maa^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Maa^{12}-Thr^{13}-Gly^{14}-Maa^{15}- Xaa$_{n2}$	47
Formula IV	4:12,7:15	Xaa$_{n1}$ - Maa ^{4}-Xaa^{5}-Xaa^{6}- Maa ^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}- Maa ^{12}-Xaa^{13}-Xaa^{14}- Maa ^{15}-Xaa$_{n2}$	48
Formula V	C4:C12,C7:C15	Asn^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-Xaa^{16}	49
Formula VI	C4:C12,C7:C15	dAsn^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-X3^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-d-Xaa^{16}	50
Formula VII	C4:C12,C7:C15	dAsn^{1}-dGlu^{2}-Asp^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-d-Xaa^{16}	51
Formula VII	C4:C12,C7:C15	dAsn^{1}-dAsp^{2}-Glu^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-d-Xaa^{16}	52
Formula VIII	C4:C12,C7:C15	dAsn^{1}-dAsp^{2}-dGlu^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Tyr^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-d-Xaa^{16}	53
Formula IX	C4:C12,C7:C15	dAsn^{1}-dGlu^{2}-dGlu^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Tyr^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-d-Xaa^{16}	54

Table II. Linaclotide and Derivatives

Name	Position of Disulfide bonds	Structure	SEQ ID NO:
SP-339 (linaclotide)	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	55
SP-340	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}	56
SP-349	C1:C6, C2:C10, C5:13	PEG3-Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}-PEG3	57
SP-353	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	58
SP-354	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Phe^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	59
SP-355	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-dTyr^{14}	60
SP-357	C1:C6, C2:C10, C5:13	PEG3-Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	61
SP-374	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	62
SP-375	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	63
SP-376	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	64
SP-377	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	65
SP-378	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	66
SP-379	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	67
SP-380	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	68
SP-381	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Phe^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	69

SP-382	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	70
SP-383	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	71
SP384	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Tyr[14]-PEG3	72
N14	C1:C6, C2:C10, C5:13	PEG3-Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-PEG3	73
N15	C1:C6, C2:C10, C5:13	PEG3-Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]	74
N16	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-PEG3	75
N17	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	76
N18	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	77
N19	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	78
N20	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	79
N21	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	80
N22	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	81
N23	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	82
N24	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	83

N25	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}-PEG3	84
N26	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Ser^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	85
N27	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Phe^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	86
N28	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Ser^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-	87
N29	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Phe^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}	88
N30	1:6, 2:10, 5:13	Pen^{1}-Pen^{2}-Glu3-Tyr^{4}-Pen^{5}-Pen^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Pen^{10}-Thr^{11}-Gly^{12}-Pen^{13}-Tyr^{14}	89
N31	1:6, 2:10, 5:13	Pen^{1}-Pen^{2}-Glu3-Tyr^{4}-Pen^{5}-Pen^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Pen^{10}-Thr^{11}-Gly^{12}-Pen^{13}	90
Formula X	C9:C14, C10:C18, C13:21	Xaa^{1}-Xaa^{2}-Xaa^{3}-Xaa^{4}-Xaa^{5}-Xaa^{6}- Asn^{7}- Tyr^{8}-Cys^{9}-Cys^{10}-Xaa^{11}-Tyr^{12}-Cys^{13}-Cys^{14}-Xaa^{15}-Xaa^{16}-Xaa^{17}-Cys^{18}- Xaa^{19}-Xaa^{20}-Cys^{21}-Xaa^{22}	91
Formula XI	C9:C14, C10:C18, C13:21	Xaa^{1}-Xaa^{2}-Xaa^{3}-Xaa^{4}-Xaa^{5}-Xaa^{6}-Asn^{7}- Phe^{8}-Cys^{9}-Cys^{10} -Xaa^{11}-Phe^{12}- Cys^{13}-Cys^{14}-Xaa^{15}-Xaa^{16}-Xaa^{17}-Cys^{18}- Xaa^{19}-Xaa^{20}-Cys^{21}-Xaa^{22}	92
Formula XII	C3:C8, C4:C12, C7:15	Asn^{1}- Phe^{2}-Cys^{3}-Cys^{4} - Xaa^{5}-Phe^{6}-Cys^{7}-Cys^{8} - Xaa^{9}-Xaa^{10}- Xaa^{11}-Cys^{12}- Xaa^{3}-Xaa^{14}-Cys^{15}-Xaa^{16}	93
Formula XIII	3:8, 4:12, C:15	Asn^{1}- Phe^{2}-Pen^{3}-Cys^{4} - Xaa^{5}-Phe^{6}-Cys^{7}-Pen^{8} - Xaa^{9}-Xaa^{10}- Xaa^{11}-Cys12- Xaa^{13}-Xaa^{14}-Cys^{15}-Xaa^{16}	94
Formula XIV	3:8, 4:12, 7:15	Asn^{1}- Phe^{2}-Maa^{3}-Maa^{4} - Xaa^{5}-Xaa^{6}-Maa^{7}-Maa^{8} - Xaa^{9}-Xaa^{10}- Xaa^{11}-Maa^{12}- Xaa^{13}-Xaa^{14}-Maa^{15}-Xaa^{16}	95
Formula XV	1:6, 2:10, 5:13	Maa^{1}-Maa^{2}-Glu3-Xaa^{4}- Maa^{5}-Maa^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Maa^{10}-Thr^{11}-Gly^{12}-Maa^{13}-Tyr^{14}	96
Formula XVI	1:6, 2:10, 5:13	Maa^{1}-Maa^{2}-Glu3-Xaa^{4}- Maa^{5}-Maa^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Maa^{10}-Thr^{11}-Gly^{12}-Maa^{13}-	97
Formula XVII	1:6, 2:10, 5:13	Xaa_{n3}-Maa^{1}-Maa^{2}-Xaa^{3}-Xaa^{4}-Maa^{5}-Maa^{6}-Xaa^{7}-Xaa^{8}-Xaa^{9}-Maa^{10}-Xaa^{11}-Xaa^{12}-Maa^{13}-Xaa_{n2}	98

Table III. GCRA Peptides

Name	Position of Disulfide bonds	Structure	SEQ ID NO:
SP-363	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu-AMIDE[16]	99
SP-364	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer[16]	100
SP-365	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer-AMIDE[16]	101
SP-366	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	102
SP-367	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr-AMIDE[16]	103
SP-373	C4:C12, C7:C15	Pyglu[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu-AMIDE[16]	104
SP-304 di PEG	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]-PEG3	105
SP-304 N-PEG	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	106
SP-304 C-PEG	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]-PEG3	107

Table IV. SP-304 Analogs, Uroguanylin , and Uroguanylin Analogs

Name	Position of Disulfide bonds	Structure	SEQ ID NO
Formula XVIII	C4:C12, C7:C15	Xaa^{1}- Xaa^{2}- Xaa^{3} -Maa^{4}-Xaa^{5}-Xaa^{6}-Maa^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Maa^{12}-Xaa^{13}-Xaa^{14}-Maa^{15}-Xaa^{16}	108
Uroguanylin	C4:C12, C7:C15	Asn^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	109
N32	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Asp^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	110
N33	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	111
N34	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Asp^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	112
N35	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	113
N36	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Asp^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	114
N37	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	115
N38	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Asp^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	116

N39	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	117
N40	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	118
N41	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	119
N42	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	120
N43	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	121
N44	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	122
N45	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	123
N46	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	124
N47	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	125
N48	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	126
N49	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	127
N50	C4:C12,	Glu^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	128

	C7:C15		
N51	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	129
N52	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	130
N53	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	131
N54	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	132
N55	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	133
N56	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	134
N57	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	135
N58	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	136
N59	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	137
N60	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	138
N61	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	139

N62	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	140
N63	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	141
N65	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	142
N66	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	143
N67	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	144
N68	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	145
N69	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	146
N70	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	147
N71	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	148
N72	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	149
N73	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	150
N74	C4:C12,	Gln^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	151

	C7:C15		
N75	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	152
N76	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	153
N77	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	154
N78	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	155
N79	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	156
N80	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	157
N81	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	158
N82	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	159
N83	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	160
N84	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	161
N85	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	162

N86	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	163
N87	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	164
N88	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	165
N89	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	166
N90	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	167
N91	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	168
N92	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	169
N93	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	170
N94	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	171
N95	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	172
N96	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	173

Table V. Guanylin and Analogs

Name	Position of Disulfide bonds	Structure	SEQ ID NO
Formula XIX	4:12,7:15	Xaa^{1}- Xaa^{2}- Xaa^{3} -Maa^{4}-Xaa^{5}-Xaa^{6}-Maa^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Maa^{12}-Xaa^{13}-Xaa^{14}-Maa^{15}	174
Guanylin	C4:C12, C7:C15	Ser^{1}-His^{2}-Thr^{3}-Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Phe^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	175
N97	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	176
N98	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	177
N99	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	178
N100	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	179
N101	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	180
N102	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	181
N103	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	182
N104	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	183
N105	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	184
N106	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	185
N107	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	186
N108	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	187

N109	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	188
N110	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	189
N111	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	190
N112	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	191
N113	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	192
N114	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	193
N115	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	194
N116	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	195
N117	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	196
N118	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	197
N119	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	198
N120	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	199
N121	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	200
N122	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	201
N123	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	202
N124	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	203
N125	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	204
N126	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	205

N127	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	206
N128	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	207

Table VI. Lymphoguanylin and Analogs

Name	Position of Disulfide bonds	Structure	SEQ ID NO
Formula XX	4:12,7:15	Xaa^{1}- Xaa^{2}- Xaa^{3} -Maa^{4}-Xaa^{5}-Xaa^{6}-Maa^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Maa^{12}-Xaa^{13}-Xaa^{14}-$Xaa_{n1}{}^{15}$	208
Lymphoguanylin	C4:C12	Gln^{1}-Glu^{2}-Glu-$^{3}Cys^{4}$-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	209
N129	C4:C12	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	210
N130	C4:C12	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	211
N131	C4:C12	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	212
N132	C4:C12	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	213
N133	C4:C12	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	214
N134	C4:C12	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	215
N135	C4:C12	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	216

N136	C4:C12	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	217
N137	C4:C12	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	218
N138	C4:C12	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	219
N139	C4:C12	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	220
N140	C4:C12	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	221
N141	C4:C12	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	222
N142	C4:C12	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	223
N143	C4:C12	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	224
N144	C4:C12	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	225
N145	C4:C12, C7:C15	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	226
N146	C4:C12, C7:C15	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	227
N147	C4:C12, C7:C15	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	228
N148	C4:C12, C7:C15	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	229
N149	C4:C12, C7:C15	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	230

N150	C4:C12, C7:C15	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser	231
N151	C4:C12, C7:C15	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	232
N152	C4:C12, C7:C15	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	233
N153	C4:C12, C7:C15	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	234
N154	C4:C12, C7:C15	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	235
N155	C4:C12, C7:C15	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	236
N156	C4:C12, C7:C15	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	237
N157	C4:C12, C7:C15	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	238
N158	C4:C12, C7:C15	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	239
N159	C4:C12, C7:C15	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	240

N160	C4:C12, C7:C15	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	241

Table VII. ST Peptide and Analogues

Name	Position of Disulfide bonds	Structure	SEQ ID NO
ST Peptide	C3:C8, C4:C12, C7:15	Asn[1]- Ser[2]-Ser[3]-Asn[4]-Ser[5]-Ser[6]-Asn[7]-Tyr[8]-Cys[9]-Cys[10]-Glu[11]-Lys[12]-Cys[13]-Cys[14]-Asn[15]-Pro[16]-Ala[17]-Cys[18]-Thr[19]-Gly[20]-Cys[21]-Tyr[22]	242
N161	C3:C8, C4:C12, C7:15	PEG3-Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	243
N162	C3:C8, C4:C12, C7:15	PEG3-Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	244
N163	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	245
N164	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	246
N165	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	247
N166	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	248
N167	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	249

1.3 Methods of Use

[122] The invention provides methods for treating or preventing gastrointestinal disorders and increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. Non-limiting examples of gastrointestinal disorders that can be treated or prevented according to the methods of the invention include irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD), ileus (*e.g.*, post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (*e.g.*, constipation associated with use of medications such as opioids, osteoarthritis drugs, or osteoporosis drugs); post surgical constipation, constipation associated with neuropathic disorders, Crohn's disease, and ulcerative colitis.

[123] In one embodiment, the invention provides methods for treating or preventing gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction, obesity, congestive heart failure, or benign prostatic hyperplasia.

[124] In one embodiment, the invention provides methods for treating or preventing constipation and/or increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining (Schiller 2001 Aliment Pharmacol Ther 15:749-763). Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease and cystic fibrosis. Constipation may also be the result of

surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

[125] In various embodiments, the constipation is associated with use of a therapeutic agent; the constipation is associated with a neuropathic disorder; the constipation is postsurgical constipation; the constipation is associated with a gastrointestinal disorder; the constipation is idiopathic (functional constipation or slow transit constipation); the constipation is associated with neuropathic, metabolic or endocrine disorder (e.g., diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease or cystic fibrosis). Constipation may also be the result of surgery or due to the use of drugs such as analgesics (e.g., opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

[126] In one embodiment, the invention provides methods for treating or preventing chronic idiopathic constipation and increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject.

[127] The term "treating" as used herein refers to a reduction, a partial improvement, amelioration, or a mitigation of at least one clinical symptom associated with the gastrointestinal disorders being treated. The term “preventing” refers to an inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorders to be prevented. The term "effective amount” as used herein refers to an amount that provides some improvement or benefit to the subject. In certain embodiments, an effective amount is an amount that provides some alleviation, mitigation, and/or decrease in at least one clinical symptom of the gastrointestinal disorder to be treated. In other embodiments, the effective amount is the amount that provides some inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorder to be prevented. The therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject. The term “subject” preferably refers to a human subject but may also refer to a non-human primate or other mammal preferably selected from among a mouse, a rat, a dog, a cat, a cow, a horse, or a pig.

[128] The invention also provides methods for treating gastrointestinal cancer in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. Non-limiting examples of gastrointestinal cancers that can be treated according to the methods of the invention include gastric cancer, esophageal cancer, pancreatic cancer, colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer.

[129] The invention also provides methods for treating lipid metabolism disorders, biliary disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders including cardiovascular disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, and obesity.

[130] Lipid metabolism disorders include, but are not limited to, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, sitosterolemia, familial hypercholesterolemia, xanthoma, combined hyperlipidemia, lecithin cholesterol acyltransferase deficiency, tangier disease, abetalipoproteinemia, erectile dysfunction, fatty liver disease, and hepatitis.

[131] Billary disorders include gallbladder disorders such as for example, gallstones, gall bladder cancer cholangitis, or primary sclerosing cholangitis; or bile duct disorders such as for example,cholecystitis, bile duct cancer or fascioliasis.

[132] Inflammatory disorders include tissue and organ inflammation such as kidney inflammation (e.g., nephritis), gastrointestinal system inflammation (e.g., Crohn's disease and ulcerative colitis); necrotizing enterocolitis (NEC); pancreatic inflammation (e.g., pancreatis), lung inflammation (e.g., bronchitis or asthma) or skin inflammation (e.g., psoriasis, eczema).

[133] Lung Disorders include for example chronic obstructive pulmonary disease (COPD), and fibrosis.

[134] Cancer includes tissue and organ carcinogenesis including metastases such as for example gastrointestinal cancer, (e.g., gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (e.g., melanoma); oral cancer; urinary tract cancer (e.g. bladder cancer or kidney cancer); blood cancer (e.g. myeloma or leukemia) or prostate cancer.

[135] Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high triglycerides. Cardiovascular disorders include for example aneurysm, angina, atherosclerosis, cerebrovascular accident (stroke), cerebrovasculardisease, congestive heart failure, coronary artery disease, myocardial infarction (heart attack), or peripheral vascular disease.

[136] Liver disorders include for example cirrhosis and fibrosis. In addition, GC-C agonist may also be useful to facilitate liver regeneration in liver transplant patients. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (e.g., periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include for example benign prostatic hyperplasia (BPH). Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

1.3.1 Therapeutically Effective Dosages

[137] Disorders are treated, prevented or alleviated by administering to a subject, *e.g.*, a mammal such as a human in need thereof, a therapeutically effective dose of a GCC agonist peptide. The present invention is based in part on the unexpected results of clinical trials in humans which demonstrated that the formulations of the invention are therapeutically effective at much lower doses than predicted based on animal studies. In accordance with one aspect of the invention, the therapeutically effective dose is between 0.01 milligrams (mg) and 10 mg per unit dose. The term "unit dose" refers to a single drug delivery entity, *e.g.*, a tablet, capsule, solution or inhalation formulation. In one embodiment, the effective dose is between 0.01 mg and 9 mg. In another embodiment, the effective dose is between 0.01 mg and 5 mg. In another embodiment, the effective dose is between 0.01 mg and 3 mg. In another embodiment, the effective dose is between 0.10 mg and 5 mg. In another embodiment, the effective dose is between 0.10 mg and 3 mg. In one embodiment, the unit dose is .01 mg, .05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 5 mg, or 10 mg. In one embodiment, the unit dose is 0.3 mg, 1.0 mg, 3.0 mg, 9.0 mg, or 9.5 mg.

[138] The GCC agonist peptides may be in a pharmaceutical composition in unit dose form, together with one or more pharmaceutically acceptable excipients. The amount of peptide present should be sufficient to have a positive therapeutic effect when administered to a patient. What constitutes a "positive therapeutic effect" will depend upon the particular condition being treated and will include any significant improvement in a condition readily recognized by one of skill in the art.

[139] The GCC agonists for use in the methods described above are preferably administered orally. Dosage forms include solutions, suspensions, emulsions, tablets, and capsules.

[140] The total daily dose can be administered to the patient in a single dose, or in multiple sub-doses. Typically, sub-doses can be administered two to six times per day, preferably two to four times per day, and even more preferably two to three times per day. Preferably, a single daily dose is administered.

[141] The GCC agonists may be administered as either the sole active agent or in combination with one or more additional active agents. In all cases, additional active agents should be administered at a dosage that is therapeutically effective using the existing art as a guide. The GCC agonists may be administered in a single composition or sequentially with the one or more additional active agents. In one embodiment, the GCC agonist is administered in combination with one or more inhibitors of cGMP dependent phosphodiesterase such as suldinac sulfone, zaprinast, motapizone, vardenafil, or sildenifil. In another embodiment, the GCC agonist is administered in combination with one or more chemotherapeutic agents. In another embodiment, the GCC agonist is administered in combination with one or more or anti-inflammatory drugs such as steroids or non-steroidal anti-inflammatory drugs (NSAIDS), such as aspirin.

[142] Combination therapy can be achieved by administering two or more agents, *e.g.*, a GCC agonist peptide described herein and another compound, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a

third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

[143] The GCC agonist peptides described herein may be combined with phosphodiesterase inhibitors, *e.g.*, sulindae sulfone, Zaprinast, sildenafil, vardenafil or tadalafil to further enhance levels of cGMP in the target tissues or organs.

[144] Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, *e.g.*, in the order X-Y- X, X-X-Y, Y-X-Y,Y-Y-X,X-X-Y-Y, etc.

1.3.2 Exemplary Agents for Combination Therapy

[145] The GCC agonist formulations of the invention may be administered alone or in combination with one or more additional therapeutic agents as part of a therapeutic regimen for the treatment or prevention of a gastrointestinal disease or disorder. In some embodiments, the GCC agonist formulation comprises one or more additional therapeutic agents. In other embodiments, the GCC agonist is formulated separately from the one or more additional therapeutic agents. In accordance with this embodiment, the GCC agonist is administered either simultaneously, sequentially, or at a different time than the one or more additional therapeutic agents. In one embodiment, the GCC agonist formulation is administered in combination with one or more additional therapeutic agents selected from the group consisting of phosphodiesterase inhibitors, cyclic nucleotides (such as cGMP and cAMP), a laxative (such as SENNA or METAMUCIL), a stool softner, an anti-tumor necrosis factor alpha therapy for IBD

(such as REMICADE, ENBREL, or HUMIRA), and anti-inflammatory drugs (such as COX-2 inhibitors, sulfasalazine, 5-ASA derivatives and NSAIDS). In certain embodiments, the GCC agonist formulation is administered in combination with an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said GCC agonist. cGMP-PDE inhibitors include, for example, suldinac sulfone, zaprinast, motapizone, vardenifil, and sildenafil. In another embodiment, the GCC agonist formulation is administered in combination with inhibitors of cyclic nucleotide transporters. Further examples of therapeutic agents that may be administered in combination with the GCC agonist formulations of the invention are given in the following sections.

1.3.2.1 Agents to Treat Gastrointestinal Cancers

[146] The GCC agonist formulations described herein can be used in combination with one or more antitumor agents including but not limited to alkylating agents, epipodophyllotoxins, nitrosoureas, anti-metabolites, vinca alkaloids, anthracycline antibiotics, nitrogen mustard agents, and the like. Particular antitumor agents include tamoxifen, taxol, etoposide, and 5-fluorouracil. In one embodiment, the GCC agonist formulations are used in combination with an antiviral agent or a monoclonal antibody.

[147] Non-limiting examples of antitumor agents that can be used in combination with the GCC agonist formulations of the invention for the treatment of colon cancer include anti-proliferative agents, agents for DNA modification or repair, DNA synthesis inhibitors, DNA/RNA transcription regulators, RNA processing inhibitors, agents that affect protein expression, synthesis and stability, agents that affect protein localization or their ability to exert their physiological action, agents that interfere with protein-protein or protein-nucleic acid interactions, agents that act by RNA interference, receptor binding molecules of any chemical nature (including small molecules and antibodies), targeted toxins, enzyme activators, enzyme inhibitors, gene regulators, HSP-90 inhibitors, molecules interfering with microtubules or other cytoskeletal components or cell adhesion and motility, agents for phototherapy, and therapy adjuncts.

[148] Representative anti-proliferative agents include N-acetyl-D-sphingosine (C.sub.2 ceramide), apigenin, berberine chloride, dichloromethylenediphosphonic acid disodium salt, loe-emodine, emodin, HA 14-1, N-hexanoyl-D-sphingosine (C.sub.6 ceramide), 7b-hydroxycholesterol, 25-hydroxycholesterol, hyperforin, parthenolide, and rapamycin.

Representative agents for DNA modification and repair include aphidicolin, bleomycin sulfate, carboplatin, carmustine, chlorambucil, cyclophosphamide monohydrate, cyclophosphamide monohydrate ISOPAC.RTM., cis-diammineplatinum(II) dichloride (Cisplatin), esculetin, melphalan, methoxyamine hydrochloride, mitomycin C, mitoxantrone dihydrochloride, oxaliplatin, and streptozocin.

[149] Representative DNA synthesis inhibitors include (.+-.)amethopterin (methotrexate), 3-amino-1,2,4-benzotriazine 1,4-dioxide, aminopterin, cytosine b-D-arabinofurdnoside (Ara-C), cytosine b-D-arabinofuranoside (Ara-C) hydrochloride, 2-fluoroadenine-9-b-D-arabinofuranoside (Fludarabine des-phosphate; F-ara-A), 5-fluoro-5'-deoxyuridinc, 5-fluorouracil, ganciclovir, hydroxyurea, 6-mercaptopurine, and 6-thioguanine.

[150] Representative DNA/RNA transcription regulators include actinomycin D, daunorubicin hydrochloride, 5,6-dichlorobenzimidazole 1-b-D-ribofuranoside, doxorubicin hydrochloride, homoharringtonine, and idarubicin hydrochloride.

[151] Representative enzyme activators and inhibitors include forskolin, DL-aminoglutethimide, apicidin, Bowman-Birk Inhibitor, butein, (S)-(+)-camptothecin, curcumin, (-)-deguelin, (-)-depudecin, doxycycline hyclate, etoposide, formestane, fostriecin sodium salt, hispidin, 2-imino-1-imidazolidineacetic acid (Cyclocreatine), oxamflatin, 4-phenylbutyric acid, roscovitine, sodium valproate, trichostatin A, tyrphostin AG 34, tyrphostin AG 879, urinary trypsin inhibitor fragment, valproic acid (2-propylpentanoic acid), and XK469.

[152] Representative gene regulators include 5-aza-2'-deoxycytidine, 5-azacytidine, cholecalciferol (Vitamin D3), ciglitizone, cyproterone acetate, 15-deoxy-D.sup.12,14-prostaglandin J.sub.2, epitestosterone, flutamide, glycyrrhizic acid ammonium salt (glycyrrhizin), 4-hydroxytamoxifen, mifepristone, procainamide hydrochloride, raloxifene hydrochloride, all trans-retinal (vitamin A aldehyde), retinoic acid (vitamin A acid), 9-cis-

retinoic acid, 13-cis-retinoic acid, retinoic acid p-hydroxyanilide, retinol (Vitamin A), tamoxifen, tamoxifen citrate salt, tetradecylthioacetic acid, and troglitazone.

[153] Representative HSP-90 inhibitors include 17-(allylamino)-17-demethoxygeldanamycin and geldanamycin.

[154] Representative microtubule inhibitors include colchicines, dolastatin 15, nocodazole, taxanes and in particular paclitaxel, podophyllotoxin, rhizoxin, vinblastine sulfate salt, vincristine sulfate salt, and vindesine sulfate salt and vinorelbine (Navelbine) ditartrate salt.

[155] Representative agents for performing phototherapy include photoactive porphyrin rings, hypericin, 5-methoxypsoralen, 8-methoxypsoralen, psoralen and ursodeoxycholic acid.

[156] Representative agents used as therapy adjuncts include amifostine, 4-amino-1,8-naphthalimide, brefeldin A, cimetidine, phosphomycin disodium salt, leuprolide (leuprorelin) acetate salt, luteinizing hormone-releasing hormone (LH-RH) acetate salt, lectin, papaverine hydrochloride, pifithrin-a, (-)-scopolamine hydrobromide, and thapsigargin.

[157] The agents can also be anti-VEGF (vascular endothelial growth factor) agents, as such are known in the art. Several antibodies and small molecules are currently in clinical trials or have been approved that function by inhibiting VEGF, such as Avastin (Bevacizumab), SU5416, SU11248 and BAY 43-9006. The agents can also be directed against growth factor receptors such as those of the EGF/Erb-B family such as EGF Receptor (Iressa or Gefitinib, and Tarceva or Erlotinib), Erb-B2, receptor (Herceptin or Trastuzumab), other receptors (such as Rituximab or Rituxan/MabThera), tyrosine kinases, non-receptor tyrosine kinases, cellular serine/threonine kinases (including MAP kinases), and various other proteins whose deregulation contribute to oncogenesis (such as small/Ras family and large/heterotrimeric G proteins). Several antibodies and small molecules targeting those molecules are currently at various stages of development (including approved for treatment or in clinical trials).

[158] In a preferred embodiment, the invention provides a method for treating colon cancer in a subject in need thereof by administering to the subject a GCC agonist formulation in combination with one or more antitumor agent selected from the group consisting of paclitaxel,

docetaxel, tamoxifen, vinorelbine, gemcitabine, cisplatin, etoposide, topotecan, irinotecan, anastrozole, rituximab, trastuzumab, fludarabine, cyclophosphamide, gentuzumab, carboplatin, interferons, and doxorubicin. In a particular embodiment the antitumor agent is paclitaxel. In a further embodiment, the method further comprises an antitumor agent selected from the group consisting of 5-FU, doxorubicin, vinorelbine, cytoxan, and cisplatin.

1.3.2.2 Agents that Treat Crohn's Disease

[159] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of Crohn's disease. Non-limiting examples of the one or more additional therapeutic agents include sulfasalazine and other mesalamine-containing drugs, generally known as 5-ASA agents, such as Asacol, Dipentum, or Pentasa, or infliximab (REMICADE). In certain embodiments, the one or more additional agents is a corticosteroid or an immunosuppressive agent such as 6-mercaptopurine or azathioprine. In another embodiment, the one or more additional agents is an antidiarrheal agent such as diphenoxylate, loperamide, or codeine.

1.3.2.3 Agents that Treat Ulcerative Colitis

[160] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of ulcerative colitis. The agents that are used to treat ulcerative colitis overlap with those used to treat Chrohn's Disease. Non-limiting examples of the one or more additional therapeutic agents that can be used in combination with a GCC agonist formulation of the invention include aminosalicylates (drugs that contain 5-aminosalicyclic acid (5-ASA)) such as sulfasalazine, olsalazine, mesalamine, and balsalazide. Other therapeutic agents that can be used include corticosteroids, such as prednisone and hydrocortisone, immunomodulators, such as azathioprine, 6-mercapto-purine (6-MP), cytokines, interleukins, and lymphokines, and anti-TNF-alpha agents, including the thiazolidinediones or glitazones such as rosiglitazone and pioglitazone. In one emobidment, the one or more additional therapeutic agents includes both cyclosporine A and 6-MP or azathioprine for the treatment of active, severe ulcerative colitis.

1.3.2.4 Agents that Treat Constipation/Irritable Bowel Syndrome

[161] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of constipation, such as that associated with irritable bowel syndrome. Non-limiting examples of the one or more additional therapeutic agents include laxatives such as SENNA, MIRALAX, LACTULOSE, PEG, or calcium polycarbophil), stool softeners (such as mineral oil or COLACE), bulking agents (such as METAMUCIL or bran), agents such as ZELNORM (also called tegaserod), and anticholinergic medications such as BENTYL and LEVSIN.

1.3.2.5 Agents for the Treatment of Postoperative Ileus

[162] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of postoperative ileus. Non-limiting examples of the one or more additional therapeutic agents include ENTEREG (alvimopan; formerly called ado lor/ ADL 8-2698), conivaptan, and related agents describes in US 6,645,959.

1.3.2.6 Anti-obesity agents

[163] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of obesity. Non-limiting examples of the one or more additional therapeutic agents include 1 lβ HSD-I (11-beta hydroxy steroid dehydrogenase type 1) inhibitors, such as BVT 3498, BVT 2733, 3-(l-adamantyl)-4-ethyl-5-(ethylthio)- 4H-l,2,4-triazole, 3-(l-adamantyl)-5-(3,4,5-trimethoxyphenyl)-4-methyl-4H-l,2,4-triazole, 3- adamantanyl-4,5,6,7,8,9,10,11,12,3a-decahydro-l,2,4-triazolo[4,3-a][l l]annulene, and those compounds disclosed in WO01/90091, WOO 1/90090, WOO 1/90092 and WO02/072084; 5HT antagonists such as those in WO03/037871, WO03/037887, and the like; 5HTIa modulators such as carbidopa, benserazide and those disclosed in US6207699, WO03/031439, and the like; 5HT2c (serotonin receptor 2c) agonists, such as BVT933, DPCA37215, IK264, PNU 22394, WAY161503, R-1065, SB 243213 (Glaxo Smith Kline) and YM 348 and those disclosed in US3914250, WO00/77010,

WO02/36596, WO02/48124, WO02/10169, WO01/66548, WO02/44152, WO02/51844, WO02/40456, and WO02/40457; 5HT6 receptor modulators, such as those in WO03/030901, WO03/035061, WO03/039547, and the like; acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al, Obesity Research, 9:202-9 (2001) and Japanese Patent Application No. JP 2000256190; anorectic bicyclic compounds such as 1426 (Aventis) and 1954 (Aventis), and the compounds disclosed in WO00/18749, WO01/32638, WO01/62746, WO01/62747, and WO03/015769; CB 1 (cannabinoid-1 receptor) antagonist/inverse agonists such as rimonabant (Acomplia; Sanofi), SR-147778 (Sanofi), SR-141716 (Sanofi), BAY 65-2520 (Bayer), and SLV 319 (Solvay), and those disclosed in patent publications US4973587, US5013837, US5081122, US5112820, US5292736, US5532237, US5624941, US6028084, US6509367, US6509367, WO96/33159, WO97/29079, WO98/31227, WO98/33765, WO98/37061, WO98/41519, WO98/43635, WO98/43636, WO99/02499, WO00/10967, WO00/10968, WO01/09120, WO01/58869, WO01/64632, WO01/64633, WO01/64634, WO01/70700, WO01/96330, WO02/076949, WO03/006007, WO03/007887, WO03/020217, WO03/026647, WO03/026648, WO03/027069, WO03/027076, WO03/027114, WO03/037332, WO03/040107, WO03/086940, WO03/084943 and EP658546; CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771 (GSK), JMV-180, A- 71378, A-71623 and SR146131 (Sanofi), and those described in US5739106; CNTF (Ciliary neurotrophic factors), such as GI- 181771 (Glaxo-SmithKline), SRl 46131 (Sanofi Synthelabo), butabindide, PD 170,292, and PD 149164 (Pfizer); CNTF derivatives, such as Axokine® (Regeneron), and those disclosed in WO94/09134, WO98/22128, and WO99/43813; dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, P 3298, TSL 225 (tryptophyl-l,2,3,4-tetrahydroisoquinoline-3- carboxylic acid; disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), TMC-2A/2B/2C, CD26 inhibtors, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, 2- cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) and the compounds disclosed patent publications. WO99/38501, WO99/46272, WO99/67279 (Probiodrug), WO99/67278 (Probiodrug), WO99/61431 (Probiodrug), WO02/083128, WO02/062764, WO03/000180, WO03/000181, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/004498, WO03/004496,WO03/017936, WO03/024942, WO03/024965, WO03/033524, WO03/037327 and EP1258476; growth hormone secretagogue

receptor agonists/antagonists, such as NN703, hexarelin, MK- 0677 (Merck), SM-130686, CP-424391 (Pfizer), LY 444,711 (Eli Lilly), L-692,429 and L- 163,255, and such as those disclosed in USSN 09/662448, US provisional application 60/203335, US6358951, US2002049196, US2002/022637, WO01/56592 and WO02/32888; H3 (histamine H3) antagonist/inverse agonists, such as thioperamide, 3-(lH-imidazol-4- yl)propyl N-(4-pentenyl)carbamate), clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and A331440, O-[3-(lH-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-32 (2001), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)), substituted N- phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., J. Med. Chem.. 43:3335-43 (2000)) and histamine H3 receptor modulators such as those disclosed in WO02/15905, WO03/024928 and WO03/024929; leptin derivatives, such as those disclosed in US5552524, US5552523, US5552522, US5521283, WO96/23513, WO96/23514, WO96/23515, WO96/23516, WO96/23517, WO96/23518, WO96/23519, and WO96/23520; leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); lipase inhibitors, such as tetrahydrolipstatin (orlistat/Xenical®), Triton WRl 339, RHC80267, lipstatin, teasaponin, diethylumbelliferyl phosphate, FL-386, WAY-121898, Bay-N-3176, valilactone, esteracin, ebelactone A, ebelactone B, and RHC 80267, and those disclosed in patent publications WO01/77094, US4598089, US4452813, USUS5512565, US5391571, US5602151, US4405644, US4189438, and US4242453; lipid metabolism modulators such as maslinic acid, erythrodiol, ursolic acid uvaol, betulinic acid, betulin, and the like and compounds disclosed in WO03/011267; Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME- 10142, ME-10145, and HS-131 (Melacure), and those disclosed in PCT publication Nos. WO99/64002, WO00/74679, WOO 1/991752, WOO 1/25192, WOO 1/52880, WOO 1/74844, WOO 1/70708, WO01/70337, WO01/91752, WO02/059095, WO02/059107, WO02/059108, WO02/059117, WO02/06276, WO02/12166, WO02/11715, WO02/12178, WO02/15909, WO02/38544, WO02/068387, WO02/068388, WO02/067869, WO02/081430, WO03/06604, WO03/007949, WO03/009847, WO03/009850, WO03/013509, and WO03/031410; Mc5r (melanocortin 5 receptor) modulators, such as those disclosed in WO97/19952, WO00/15826, WO00/15790, US20030092041; melanin-concentrating hormone 1

receptor (MCHR) antagonists, such as T-226296 (Takeda), SB 568849, SNP-7941 (Synaptic), and those disclosed in patent publications WOO 1/21169, WO01/82925, WO01/87834, WO02/051809, WO02/06245, WO02/076929, WO02/076947, WO02/04433, WO02/51809, WO02/083134, WO02/094799, WO03/004027, WO03/13574, WO03/15769, WO03/028641, WO03/035624, WO03/033476, WO03/033480, JP13226269, and JP1437059; mGluR5 modulators such as those disclosed in WO03/029210, WO03/047581, WO03/048137, WO03/051315, WO03/051833, WO03/053922, WO03/059904, and the like; serotoninergic agents, such as fenfluramine (such as Pondimin® (Benzeneethanamine, N-ethyl- alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Robbins), dexfenfluramine (such as Redux® (Benzeneethanamine, N-ethyl-alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Interneuron) and sibutramine ((Meridia®, Knoll/Reductil™) including racemic mixtures, as optically pure isomers (+) and (-), and pharmaceutically acceptable salts, solvents, hydrates, clathrates and prodrugs thereof including sibutramine hydrochloride monohydrate salts thereof, and those compounds disclosed in US4746680, US4806570, and US5436272, US20020006964, WOO 1/27068, and WOO 1/62341; NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; NPY 1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI- 264879A, and those disclosed in US6001836, WO96/14307, WO01/23387, WO99/51600, WO01/85690, WO01/85098, WO01/85173, and WO01/89528; NPY5 (neuropeptide Y Y5) antagonists, such as 152,804, GW-569180A, GW-594884A, GW- 587081X, GW-548118X, FR235208, FR226928, FR240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, LY-366377, PD-160170, SR- 120562A, SR-120819A, JCF-104, and H409/22 and those compounds disclosed in patent publications US6140354, US6191160, US6218408, US6258837, US6313298, US6326375, US6329395, US6335345, US6337332, US6329395, US6340683, EP01010691, EP-01044970, WO97/19682, WO97/20820, WO97/20821, WO97/20822, WO97/20823, WO98/27063, WO00/107409, WO00/185714, WO00/185730, WO00/64880, WO00/68197, WO00/69849, WO/0113917, WO01/09120, WO01/14376, WO01/85714, WO01/85730, WO01/07409, WO01/02379, WO01/23388, WO01/23389, WOO 1/44201, WO01/62737, WO01/62738, WO01/09120, WO02/20488, WO02/22592, WO02/48152, WO02/49648, WO02/051806, WO02/094789, WO03/009845, WO03/014083, WO03/022849, WO03/028726 and Norman et al, J. Med. Chem. 43:4288-4312 (2000); opioid antagonists, such as nalmefene (REVEX ®), 3-methoxynaltrexone,

methylnaltrexone, naloxone, and naltrexone (e.g. PT901; Pain Therapeutics, Inc.) and those disclosed in US20050004155 and WO00/21509; orexin antagonists, such as SB-334867-A and those disclosed in patent publications WO01/96302, WO01/68609, WO02/44172, WO02/51232, WO02/51838, WO02/089800, WO02/090355, WO03/023561, WO03/032991, and WO03/037847; PDE inhibitors (e.g. compounds which slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and cGMP; possible PDE inhibitors are primarily those substances which are to be numbered among the class consisting of the PDE3 inhibitors, the class consisting of the PDE4 inhibitors and/or the class consisting of the PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors) such as those disclosed in patent publications DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EPOl 12987, EPOl 16948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, US4963561, US5141931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DEl 116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6331543, US20050004222 (including those disclosed in formulas I- XIII and paragraphs 37-39, 85-0545 and 557-577), WO9307124, EP0163965, EP0393500, EP0510562,

EP0553174, WO9501338 and WO9603399, as well as PDE5 inhibitors (such as RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra™)), PDE4 inhibitors (such as etazolate, ICI63197, RP73401, imazolidinone (RO-20-1724), MEM 1414 (R1533/R1500; Pharmacia Roche), denbufylline, rolipram, oxagrelate, nitraquazone, Y-590, DH-6471, SKF-94120, motapizone, lixazinone, indolidan, olprinone, atizoram, KS-506-G, dipamfylline, BMY-43351, atizoram, arofylline, filaminast, PDB-093, UCB-29646, CDP-840, SKF-107806, piclamilast, RS-17597, RS-25344- 000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, mopidamol, anagrelide, ibudilast, amrinone, pimobendan, cilostazol, quazinone and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide, PDE3 inhibitors (such as ICI153, 100, bemorandane (RWJ 22867), MCI-154, UD-CG 212, sulmazole, ampizone, cilostamide, carbazeran, piroximone, imazodan, CI-930, siguazodan, adibendan, saterinone, SKF-95654, SDZ-MKS-492, 349-U-85, emoradan, EMD-53998, EMD- 57033, NSP-306, NSP-307, revizinone, NM-702, WIN-62582 and WIN-63291, enoximone and milrinone, PDE3/4 inhibitors (such as benafentrine, trequinsin, ORG-30029, zardaverine, L- 686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and tolafentrine) and other PDE inhibitors (such as vinpocetin, papaverine, enprofylline, cilomilast, fenoximone, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®); Neuropeptide Y2 (NPY2) agonists include but are not limited to: polypeptide YY and fragments and variants thereof (e.g. YY3-36 (PYY3-36)(N. Engl. J. Med. 349:941, 2003; IKPEAPGE DASPEELNRY YASLRHYLNL VTRQRY (SEQ ID NO:XXX)) and PYY agonists such as those disclosed in WO02/47712, WO03/026591, WO03/057235, and WO03/027637; serotonin reuptake inhibitors, such as, paroxetine, fluoxetine (Prozac™), fluvoxamine, sertraline, citalopram, and imipramine, and those disclosed in US6162805, US6365633, WO03/00663, WOO 1/27060, and WOO 1/162341; thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in WO02/15845, WO97/21993, WO99/00353, GB98/284425, U.S. Provisional Application No. 60/183,223, and Japanese Patent Application No. JP 2000256190; UCP-I (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5, 6,7,8- tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-l-propenyl]benzoic acid (TTNPB), retinoic acid, and those disclosed in WO99/00123; β3 (beta adrenergic receptor 3) agonists, such as AJ9677/TAK677 (Dainippon/Takeda), L750355 (Merck), CP331648 (Pfizer), CL-316,243, SB 418790, BRL-

37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GW 427353, Trecadrine, Zeneca D7114, N-5984 (Nisshin Kyorin), LY-377604 (Lilly), SR 59119A, and those disclosed in US5541204, US5770615, US5491134, US5776983, US488064, US5705515, US5451677, WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753, WO01/74782, WO02/32897, WO03/014113, WO03/016276, WO03/016307, WO03/024948, WO03/024953 and WO03/037881; noradrenergic agents including, but not limited to, diethylpropion (such as Tenuate® (1- propanone, 2-(diethylamino)-l -phenyl-, hydrochloride), Merrell), dextroamphetamine (also known as dextroamphetamine sulfate, dexamphetamine, dexedrine, Dexampex, Ferndex, Oxydess II, Robese, Spancap #1), mazindol ((or 5-(p-chlorophenyl)-2,5-dihydro-3H- imidazo[2,l-a]isoindol-5-ol) such as Sanorex®, Novartis or Mazanor®, Wyeth Ayerst), phenylpropanolamine (or Benzenemethanol, alpha-(l-aminoethyl)-, hydrochloride), phentermine ((or Phenol, 3-[[4,5-duhydro-lH-imidazol-2-yl)ethyl](4-methylpheny-l)amino], monohydrochloride) such as Adipex-P®, Lemmon, FASTIN®, Smith-Kline Beecham and Ionamin®, Medeva), phendimetrazine ((or (2S,3S)-3,4-Dimethyl-2phenylmorpholine L-(+)- tartrate (1 :1)) such as Metra® (Forest) , Plegine® (Wyeth- Ay erst), Prelu-2® (Boehringer Ingelheim), and Statobex® (Lemmon), phendamine tartrate (such as Thephorin® (2,3,4,9- Tetrahydro-2-methyl-9-phenyl-lH-indenol[2,l-c]pyridine L-(+)-tartrate (1 :1)), Hoffmann- LaRoche), methamphetamine (such as Desoxyn®, Abbot ((S)-N, (alpha)-dimethylbenzeneethanamine hydrochloride)), and phendimetrazine tartrate (such as Bontril® Slow-Release Capsules, Amarin (-3,4-Dimethyl-2-phenylmorpholine Tartrate); fatty acid oxidation upregulator/inducers such as Famoxin® (Genset); monamine oxidase inhibitors including but not limited to befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, toloxatone, pirlindol, amiflamine, sercloremine, bazinaprine, lazabemide, milacemide, caroxazone and other certain compounds as disclosed by WO01/12176; and other anti-obesity agents such as 5HT-2 agonists, ACC (acetyl-CoA carboxylase) inhibitors such as those described in WO03/072197, alpha-lipoic acid (alpha-LA), AOD9604, appetite suppressants such as those in WO03/40107, ATL-962 (Alizyme PLC), benzocaine, benzphetamine hydrochloride (Didrex), bladderwrack (focus vesiculosus), BRS3 (bombesin receptor subtype 3) agonists, bupropion, caffeine, CCK agonists, chitosan, chromium, conjugated linoleic acid, corticotropin-releasing hormone agonists, dehydroepiandrosterone, DGATl (diacylglycerol acyltransferase 1) inhibitors, DGAT2 (diacylglycerol acyltransferase 2) inhibitors, dicarboxylate transporter inhibitors,

ephedra, exendin-4 (an inhibitor of glp-1) FAS (fatty acid synthase) inhibitors (such as Cerulenin and C75), fat resorption inhibitors (such as those in WO03/053451, and the like), fatty acid transporter inhibitors, natural water soluble fibers (such as psyllium, plantago, guar, oat, pectin), galanin antagonists, galega (Goat's Rue, French Lilac), garcinia cambogia, germander (teucrium chamaedrys), ghrelin antibodies and ghrelin antagonists (such as those disclosed in WO01/87335, and WO02/08250), polypeptide hormones and variants thereof which affect the islet cell secretion, such as the hormones of the secretin/gastric inhibitory polypeptide (GIP)/vasoactive intestinal polypeptide (VIP)/pituitary adenylate cyclase activating polypeptide (PACAP)/glucagon-like polypeptide II (GLP- II)/glicentin/glucagon gene family and/or those of the adrenomedullin/amylin/calcitonin gene related polypeptide (CGRP) gene family includingGLP-1 (glucagon- like polypeptide 1) agonists (e.g. (1) exendin-4, (2) those GLP-I molecules described in US20050130891 including GLP- 1(7-34), GLP-l(7-35), GLP-l(7-36) or GLP-l(7-37) in its C-terminally carboxylated or amidated form or as modified GLP-I polypeptides and modifications thereof including those described in paragraphs 17-44 of US20050130891, and derivatives derived from GLP-l-(7- 34)COOH and the corresponding acid amide are employed which have the following general formula: R-NH-HAEGTFTSDVSYLEGQAAKEFIAWLVK-$CONH_2$ wherein R=H or an organic compound having from 1 to 10 carbon atoms. Preferably, R is the residue of a carboxylic acid. Particularly preferred are the following carboxylic acid residues: formyl, acetyl, propionyl, isopropionyl, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert- butyl.) and glp-1 (glucagon-like polypeptide- 1), glucocorticoid antagonists, glucose transporter inhibitors, growth hormone secretagogues (such as those disclosed and specifically described in US5536716), interleukin-6 (IL-6) and modulators thereof (as in WO03/057237, and the like), L- carnitine, Mc3r (melanocortin 3 receptor) agonists, MCH2R (melanin concentrating hormone 2R) agonist/antagonists, melanin concentrating hormone antagonists, melanocortin agonists (such as Melanotan II or those described in WO 99/64002 and WO 00/74679), nomame herba, phosphate transporter inhibitors, phytopharm compound 57 (CP 644,673), pyruvate, SCD-I (stearoyl-CoA desaturase-1) inhibitors, T71 (Tularik, Inc., Boulder CO), Topiramate (Topimax®, indicated as an anti-convulsant which has been shown to increase weight loss), transcription factor modulators (such as those disclosed in WO03/026576), β-hydroxy steroid dehydrogenase- 1 inhibitors (β -HSD-I), β-hydroxy-β-methylbutyrate, p57 (Pfizer), Zonisamide (Zonegran™,

indicated as an anti-epileptic which has been shown to lead to weight loss), and the agents disclosed in US20030119428 paragraphs 20-26.

1.3.2.7 Phosphodiesterase inhibitors

[164] In certain embodiments, the regimen of combination therapy includes the administration of one or more phosphodiesterase ("PDE") inhibitors. PDE inhibitors slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibiting phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and/or cGMP. Non-limiting examples of PDE inhibitors that can be used in combination with the GCC agonists of the invention include PDE3 inhibitors, PDE4 inhibitors and/or PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors. Non-limiting examples of such PDE inhibitors are described in the following patent applications and patents: DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EPOl 12987, EPOl 16948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, U.S. Pat. Nos. 4,963,561, 5,141,931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DEl 116676, DE2162096,

EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6,331,543, US20050004222 (including those disclosed in formulas I-XIII and paragraphs 37-39, 85-0545 and 557-577) and WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399. PDE5 inhibitors which may be mentioned by way of example are RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra®). PDE4 inhibitors which may be mentioned by way of example are RO-20-1724, MEM 1414 (R1533/R1500; Pharmacia Roche), DENBUFYLLINE, ROLIPRAM, OXAGRELATE, NITRAQUAZONE, Y-590, DH-6471, SKF-94120, MOTAPIZONE, LIXAZINONE, INDOLIDAN, OLPRINONE, ATIZORAM, KS-506-G, DIPAMFYLLINE, BMY-43351, ATIZORAM, AROFYLLINE, FILAMINAST, PDB-093, UCB-29646, CDP-840, SKF- 107806, PICLAMILAST, RS- 17597, RS-25344-000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, MOPIDAMOL, ANAGRELIDE, IBUDILAST, AMRINONE, PIMOBENDAN, CILOSTAZOL, QUAZINONE and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide. PDE3 inhibitors which may be mentioned by way of example are SULMAZOLE, AMPIZONE, CILOSTAMIDE, CARBAZERAN, PIROXIMONE, IMAZODAN, CI-930, SIGUAZODAN, ADIBENDAN, SATERINONE, SKF-95654, SDZ-MKS-492, 349-U-85, EMORADAN, EMD-53998, EMD-57033, NSP-306, NSP-307, REVIZINONE, NM-702, WIN-62582 and WIN-63291, ENOXIMONE and MILRINONE. PDE3/4 inhibitors which may be mentioned by way of example are BENAFENTRINE, TREQUINSIN, ORG-30029, ZARDAVERINE, L-686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and TOLAFENTRINE. Other PDE inhibitors include: cilomilast, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®), zaprinast (PDE5 specific). GCC AGONIST

1.3.2.8 Analgesic Agents

[165] In certain embodiments, the regimen of combination therapy includes the administration of one or more analgesic agents, *e.g.*, an analgesic compound or an analgesic polypeptide. In some embodiments, the GCC agonist formulation is administered simultaneously or sequentially with one or more analgesic agents. In other embodiments, the GCC agonist is covalently linked or attached to an analgesic agent to create a therapeutic conjugate. Non-limiting examples of

analgesic agents that can be used include calcium channel blockers, 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HTl receptor antagonists), opioid receptor agonists (loperamide, fedotozine, and fentanyl), NKl receptor antagonists, CCK receptor agonists (*e.g.*, loxiglumide), NKl receptor antagonists, NK3 receptor antagonists, norepinephrine-serotonin reuptake inhibitors (NSRI), vanilloid and cannabanoid receptor agonists, and sialorphin. Further examples of analgesic agents in the various classes are known in the art.

[166] In one embodiment, the analgesic agent is an analgesic polypeptide selected from the group consisting of sialorphin-related polypeptides, including those comprising the amino acid sequence QHNPR (SEQ ID NO: 239), including: VQHNPR (SEQ ID NO: 240); VRQHNPR (SEQ ID NO: 241); VRGQHNPR (SEQ ID NO: 242); VRGPQHNPR (SEQ ID NO: 243); VRGPRQHNPR (SEQ ID NO: 244); VRGPRRQHNPR (SEQ ID NO: 245); and RQHNPR (SEQ ID NO: 246). Sialorphin-related polypeptides bind to neprilysin and inhibit neprilysin-mediated breakdown of substance P and Met-enkephalin. Thus, compounds or polypeptides that are inhibitors of neprilysin are useful analgesic agents which can be administered with the GCC agonists described herein or covalently linked to a GCC agonist to form a therapeutic conjugate. Sialorphin and related polypeptides are described in U.S. Patent 6,589,750; U.S. 20030078200 Al; and WO 02/051435 A2.

[167] In another embodiment, a GCC agonist formulation of the invention is administered as part of a regimen of combination therapy with an opioid receptor antagonist or agonist. In one embodiment, the GCC agonist and the opioid receptor antagonist or agonist are linked via a covalent bond. Non-limiting examples of opioid receptor antagonists include naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, nor-binaltorphimine, enkephalin pentapeptide (HOE825; Tyr-D-Lys-Gly-Phe-L-homoserine), trimebutine, vasoactive intestinal polypeptide, gastrin, glucagons. Non-limiting examples of opioid receptor agonists include fedotozine, asimadoline, and ketocyclazocine, the compounds described in WO03/097051 and WO05/007626, morphine, diphenyloxylate, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH 2; WO 01/019849 Al), and loperamide.

[168] Further non-limiting examples of analgesic agents that can be used in a regimen of combination therapy along with the GCC agonist formulations of the invention include the

dipeptide Tyr-Arg (kyotorphin); the chromogranin-derived polypeptide (CgA 47-66; *See, e.g.*, Ghia et al. 2004 Regulatory polypeptides 119:199); CCK receptor agonists such as caerulein; conotoxin polypeptides; peptide analogs of thymulin (FR Application 2830451); CCK (CCKa or CCKb) receptor antagonists, including loxiglumide and dexloxiglumide (the R- isomer of loxiglumide) (WO 88/05774); 5-HT4 agonists such as tegaserod (Zelnorm®), mosapride, metoclopramide, zacopride, cisapride, renzapride, benzimidazolone derivatives such as BIMU 1 and BIMU 8, and lirexapride; calcium channel blockers such as ziconotide and related compounds described in, for example, EP625162B1, US 5,364,842, US 5,587,454, US 5,824,645, US 5,859,186, US 5,994,305, US 6087,091, US 6,136,786, WO 93/13128 Al, EP 1336409 Al, EP 835126 Al, EP 835126 Bl, US 5,795,864, US 5,891,849, US 6,054,429, WO 97/01351 Al; NK-I, receptor antagonists such as aprepitant (Merck & Co Inc), vofopitant, ezlopitant (Pfizer, Inc.), R-673 (Hoffmann-La Roche Ltd), SR-48968 (Sanofi Synthelabo), CP-122,721 (Pfizer, Inc.), GW679769 (Glaxo Smith Kline), TAK-637 (Takeda/Abbot), SR-14033, and related compounds described in, for example, EP 873753 Al, US 20010006972 Al, US 20030109417 Al, WO 01/52844 Al (for a review see Giardina et al. 2003.Drugs 6:758); NK-2 receptor antagonists such as nepadutant (Menarini Ricerche SpA), saredutant (Sanofi-Synthelabo), GW597599 (Glaxo Smith Kline), SR-144190 (Sanofi-Synthelabo) and UK-290795 (Pfizer Inc); NK3 receptor antagonists such as osanetant (SR-142801; Sanofi-Synthelabo), SSR-241586, talnetant and related compounds described in, for example, WO 02/094187 A2, EP 876347 Al, WO 97/21680 Al, US 6,277,862, WO 98/1 1090, WO 95/28418, WO 97/19927, and Boden et al. (J Med Chem. 39:1664-75, 1996); norepinephrine-serotonin reuptake inhibitors (NSRI) such as milnacipran and related compounds described in WO 03/077897; and vanilloid receptor antagonists such as arvanil and related compouds described in WO 01/64212 Al.

[169] In addition to sialorphin-related polypeptides, analgesic polypeptides include: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, ziconotide, and substance P.

1.3.2.9 Insulin and Insulin Modulating Agents

[170] The GCC agonist peptides described herein can be used in combination therapy with insulin and related compounds including primate, rodent, or rabbit insulin including biologically active variants thereof including allelic variants, more preferably human insulin available in

recombinant form. Sources of human insulin include pharmaceutically acceptable and sterile formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin™ (human insulin rDNA origin). See, the THE PHYSICIAN'S DESK REFERENCE, 55.sup.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins).

[171] The GCC peptides described herein can also be used in combination therapy with agents that can boost insulin effects or levels of a subject upon administration, e.g. glipizide and/or rosiglitazone. The polypeptides and agonistsdescribed herein can be used in combitherapy with SYMLIN® (pramlintide acetate) and Exenatide® (synthetic exendin-4; a 39 aa polypeptide).

1.3.2.10 Anti-Hypertensive Agents

[172] The GCC agonist peptides described herein can be used in combination therapy with an anti-hypertensive agent including but not limited to: (1) diuretics, such as thiazides, including chlorthalidone, chlorthiazide, dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, and hydrochlorothiazide; loop diuretics, such as bumetanide, ethacrynic acid, furosemide, and torsemide; potassium sparing agents, such as amiloride, and triamterene; carbonic anhydrase inhibitors, osmotics(such as glycerin) and aldosterone antagonists, such as spironolactone, epirenone, and the like; (2) beta-adrenergic blockers such as acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol, and timolol, and the like; (3) calcium channel blockers such as amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, diltiazem, efonidipine, felodipine, gallopamil, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodepine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil, and the like; (4) angiotensin converting enzyme (ACE) inhibitors such as benazepril; captopril; ceranapril; cilazapril; delapril; enalapril; enalopril; fosinopril; imidapril; lisinopril; losinopril; moexipril; quinapril; quinaprilat; ramipril; perindopril; perindropril; quanipril; spirapril; tenocapril; trandolapril, and zofenopril, and the like; (5) neutral endopeptidase inhibitors such as omapatrilat, cadoxatril and ecadotril, fosidotril, sampatrilat, AVE7688, ER4030, and the like; (6) endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; (7) vasodilators such as hydralazine, clonidine, minoxidil, and nicotinyl alcohol, and the like; (8)

angiotensin II receptor antagonists such as aprosartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, pratosartan, tasosartan, telmisartan, valsartan, and EXP-3137, FI6828K, and RNH6270, and the like; (9) α/β adrenergic blockers such as nipradilol, arotinolol and amosulalol, and the like; (10) alpha 1 blockers, such as terazosin, urapidil, prazosin, tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, and XENOlO, and the like; (11) alpha 2 agonists such as lofexidine, tiamenidine, moxonidine, rilmenidine and guanobenz, and the like; (12) aldosterone inhibitors, and the like; and (13) angiopoietin-2 -binding agents such as those disclosed in WO03/030833. Specific anti-hypertensive agents that can be used in combination with polypeptides and agonists described herein include, but are not limited to: diuretics, such as thiazides (e.g., chlorthalidone, cyclothiazide (CAS RN 2259-96-3), chlorothiazide (CAS RN 72956-09-3, which may be prepared as disclosed in US2809194), dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, bendroflumethazide, methyclothazide, polythiazide, trichlormethazide, chlorthalidone, indapamide, metolazone, quinethazone, althiazide (CAS RN 5588-16-9, which may be prepared as disclosed in British Patent No. 902,658), benzthiazide (CAS RN 91-33-8, which may be prepared as disclosed in US3108097), buthiazide (which may be prepared as disclosed in British Patent Nos. 861 ,367), and hydrochlorothiazide), loop diuretics (e.g. bumetanide, ethacrynic acid, furosemide, and torasemide), potassium sparing agents (e.g. amiloride, and triamterene (CAS Number 396-01-O)), and aldosterone antagonists (e.g. spironolactone (CAS Number 52-01-7), epirenone, and the like); β-adrenergic blockers such as Amiodarone (Cordarone, Pacerone), bunolol hydrochloride (CAS RN 31969-05-8, Parke-Davis), acebutolol (±N-[3-Acetyl-4-[2-hydroxy-3-[(l methylethyl)amino]propoxy]phenyl]-butanamide, or (±)-3'-Acetyl-4'-[2-hydroxy -3-(isopropylamino) propoxy] butyranilide), acebutolol hydrochloride (e.g. Sectral®, Wyeth-Ayerst), alprenolol hydrochloride (CAS RN 13707-88-5 see Netherlands Patent Application No. 6,605,692), atenolol (e.g. Tenormin®, AstraZeneca), carteolol hydrochloride (e.g. Cartrol® Filmtab®, Abbott), Celiprolol hydrochloride (CAS RN 57470-78-7, also see in US4034009), cetamolol hydrochloride (CAS RN 77590-95-5, see also US4059622), labetalol hydrochloride (e.g. Normodyne®, Schering), esmolol hydrochloride (e.g. Brevibloc®, Baxter), levobetaxolol hydrochloride (e.g. Betaxon™ Ophthalmic Suspension, Alcon), levobunolol hydrochloride (e.g. Betagan® Liquifilm® with C CAP® Compliance Cap, Allergan), nadolol (e.g. Nadolol, Mylan), practolol (CAS RN 6673-35-4, see also US3408387), propranolol hydrochloride (CAS RN 318-

98-9), sotalol hydrochloride (e.g. Betapace AF™,Berlex), timolol (2-Propanol,l-[(l,l-dimethylethyl)amino]-3-[[4-4(4-morpholinyl)-l,2,5-thiadiazol-3-yl]oxy]-, hemihydrate, (S)-, CAS RN 91524-16-2), timolol maleate (S)-I -[(1,1 -dimethylethyl) amino]-3-[[4- (4-morpholinyl)-l,2,5-thiadiazol -3- yl] oxy]-2-propanol (Z)-2-butenedioate (1 :1) salt, CAS RN 26921-17-5), bisoprolol (2-Propanol, l-[4-[[2-(l-methylethoxy)ethoxy]-methyl]phenoxyl]-3-[(l-meth- ylethyl)amino]-, (±), CAS RN 66722-44-9), bisoprolol fumarate (such as (±)-l-[4-[[2-(l-Methylethoxy) ethoxy]methyl]phenoxy]-3-[(l-methylethyl)amino]-2-propanol (E) -2-butenedioate (2:1) (salt), e.g., Zebeta™ , Lederle Consumer), nebivalol (2H-l-Benzopyran-2-methanol, αα'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-, CAS RN 99200-09-6 see also U.S. Pat. No. 4,654,362), cicloprolol hydrochloride, such 2-Propanol, l-[4-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-[l-methylethyl)amino]-, hydrochloride, A.A.S. RN 63686-79-3), dexpropranolol hydrochloride (2-Propanol,l-[l-methylethy)-amino]-3-(l-naphthalenyloxy)-hydrochloride (CAS RN 13071-11-9), diacetolol hydrochloride (Acetamide, N-[3-acetyl-4-[2-hydroxy-3-[(l-methyl-ethyl)amino]propoxy] [phenyl]-, monohydrochloride CAS RN 69796-04-9), dilevalol hydrochloride (Benzamide, 2-hydroxy-5-[l-hydroxy-2-[l-methyl-3-phenylpropyl)amino]ethyl]-, monohydrochloride, CAS RN 75659-08-4), exaprolol hydrochloride (2-Propanol, 1 -(2-cyclohexylphenoxy)-3 - [(1 -methylethyl)amino] -, hydrochloride CAS RN 59333-90-3), flestolol sulfate (Benzoic acid, 2-fluro-,3-[[2-[aminocarbonyl)amino]- - dimethylethyl]amino]-2-hydroxypropyl ester, (+)- sulfate (1 :1) (salt), CAS RN 88844-73-9; metalol hydrochloride (Methanesulfonamide, N-[4-[l-hydroxy-2-(methylamino)propyl]phenyl]-, monohydrochloride CAS RN 7701-65-7), metoprolol 2-Propanol, l-[4-(2- methoxyethyl)phenoxy]-3-[l-methylethyl)amino]-; CAS RN 37350-58-6), metoprolol tartrate (such as 2-Propanol, l-[4-(2-methoxyethyl)phenoxy]-3-[(l-methylethyl)amino]-, e.g., Lopressor®, Novartis), pamatolol sulfate (Carbamic acid, [2-[4-[2-hydroxy-3-[(l- methylethyl)amino]propoxyl]phenyl]-ethyl]-, methyl ester, (±) sulfate (salt) (2:1), CAS RN 59954-01-7), penbutolol sulfate (2-Propanol, l-(2-cyclopentylphenoxy)-3-[l,l-dimethyle- thyl)amino] 1 , (S)-, sulfate (2:1) (salt), CAS RN 38363-32-5), practolol (Acetamide, N-[4-[2- hydroxy-3-[(l-methylethyl)amino]-propoxy]phenyl]-, CAS RN 6673-35-4;) tiprenolol hydrochloride (Propanol, l-[(l-methylethyl)amino]-3-[2-(methylthio)-phenoxy]-, hydrochloride, (±), CAS RN 39832-43-4), tolamolol (Benzamide, 4-[2-[[2-hydroxy-3-(2-methylphenoxy)-propyl] amino] ethoxyl]-, CAS RN 38103-61-6), bopindolol, indenolol, pindolol, propanolol,

tertatolol, and tilisolol, and the like; calcium channel blockers such as besylate salt of amlodipine (such as 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-l ,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate, e.g., Norvasc®, Pfizer), clentiazem maleate (1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-(2S-cis)-, (Z)-2-butenedioate (1 :1), see also US4567195), isradipine (3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-l,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester, (±)-4(4-benzofurazanyl)- 1 ,4-dihydro-2,6-dimethyl-3 ,5 -pyridinedicarboxylate, see also US4466972); nimodipine (such as is isopropyl (2- methoxyethyl) 1, 4- dihydro -2,6- dimethyl -4- (3-nitrophenyl) -3,5- pyridine - dicarboxylate, e.g. Nimotop®, Bayer), felodipine (such as ethyl methyl 4-(2,3-dichlorophenyl)-l,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate- , e.g. Plendil® Extended-Release, AstraZeneca LP), nilvadipine (3,5-Pyridinedicarboxylic acid, 2-cyano-l,4-dihydro-6-methyl-4-(3-nitrophenyl)-,3-methyl 5-(l-methylethyl) ester, also see US3799934), nifedipine (such as 3, 5 -pyridinedicarboxylic acid,l,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, e.g., Procardia XL® Extended Release Tablets, Pfizer), diltiazem hydrochloride (such as l,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis., e.g., Tiazac®, Forest), verapamil hydrochloride (such as benzeneacetronitrile, (alpha)-[[3-[[2-(3,4-dimethoxyphenyl) ethyl]methylamino]propyl] -3 ,4-dimethoxy-(alpha)-(1 -methylethyl) hydrochloride, e.g., Isoptin® SR, Knoll Labs), teludipine hydrochloride (3,5-Pyridinedicarboxylic acid, 2-[(dimethylamino)methyl]4-[2-[(lE)-3-(l,l-dimethylethoxy)-3-oxo- l-propenyl]phenyl]-l,4-dihydro-6-methyl-, diethyl ester, monohydrochloride) CAS RN 108700-03-4), belfosdil (Phosphonic acid, [2-(2-phenoxy ethyl)- 1,3 -propane- diyl]bis-, tetrabutyl ester CAS RN 103486-79-9), fostedil (Phosphonic acid, [[4-(2-benzothiazolyl)phenyl]methyl]-, diethyl ester CAS RN 75889-62-2), aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, efonidipine, gallopamil, lacidipine, lemildipine, lercanidipine, monatepil maleate (1-Piperazinebutanamide, N-(6, 11 -dihydrodibenzo(b,e)thiepin- 11 -yl)4-(4-fluorophenyl)-, (+)-, (Z)-2-butenedioate (1 :1) (±)-N-(6,l l-Dihydrodibenzo(b,e)thiep- in-l l-yl)-4-(p- fluorophenyl)-l-piperazinebutyramide maleate (1 :1) CAS RN 132046-06-1), nicardipine, nisoldipine, nitrendipine, manidipine, pranidipine, and the like; T-channel calcium antagonists such as mibefradil; angiotensin converting enzyme (ACE) inhibitors such as benazepril, benazepril hydrochloride (such as 3-[[l-(ethoxycarbonyl)-3- phenyl-(1 S)-propyl]amino]-2,3

,4,5-tetrahydro-2-oxo- 1 H - 1 -(3 S)-benzazepine- 1 -acetic acid monohydrochloride, e.g., Lotrel®, Novartis), captopril (such as l-[(2S)-3-mercapto-2- methylpropionyl]-L-proline, e.g., Captopril, Mylan, CAS RN 62571-86-2 and others disclosed in US4046889), ceranapril (and others disclosed in US4452790), cetapril (alacepril, Dainippon disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986)), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987), indalapril (delapril hydrochloride (2H-1,2,4- Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1- dioxide CAS RN 2259-96-3); disclosed in US4385051), enalapril (and others disclosed in US4374829), enalopril, enaloprilat, fosinopril, ((such as L-proline, 4-cyclohexyl-l-[[[2-methyl- l-(l-oxopropoxy) propoxy](4-phenylbutyl) phosphinyl]acetyl]-, sodium salt, e.g., Monopril, Bristol-Myers Squibb and others disclosed in US4168267), fosinopril sodium (L- Proline, 4-cyclohexyl-l-[[(R)-[(lS)-2-methyl-l-(l-ox- opropoxy)propox), imidapril, indolapril (Schering, disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983)), lisinopril (Merck), losinopril, moexipril, moexipril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(lS)- 1 -(ethoxycarbonyl)-3-phenylpropyl]amino]- 1 -oxopropyl]- 1 ,- 2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, (3S)- CAS RN 82586-52-5), quinapril, quinaprilat, ramipril (Hoechsst) disclosed in EP 79022 and Curr. Ther. Res. 40:74 (1986), perindopril erbumine (such as 2S,3aS,7aS- 1 -[(S)-N-[(S)- 1 -Carboxybutyljalanyljhexahydro^-indolinecarboxylic acid, 1 -ethyl ester, compound with tert-butylamine (1 :1), e.g., Aceon®, Solvay), perindopril (Servier, disclosed in Eur. J. clin. Pharmacol. 31 :519 (1987)), quanipril (disclosed in US4344949), spirapril (Schering, disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5): 173 (1986)), tenocapril, trandolapril, zofenopril (and others disclosed in US4316906), rentiapril (fentiapril, disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983)), pivopril, YS980, teprotide (Bradykinin potentiator BPP9a CAS RN 35115-60-7), BRL 36,378 (Smith Kline Beecham, see EP80822 and EP60668), MC-838 (Chugai, see CA. 102:72588v and Jap. J. Pharmacol. 40:373 (1986), CGS 14824 (Ciba-Geigy, 3-([l-ethoxycarbonyl-3-phenyl-(lS)-propyl]amino)-2,3,4,5-tetrahydro-2-ox- o-l-(3S)-benzazepine-l acetic acid HCl, see U.K. Patent No. 2103614), CGS 16,617 (Ciba- Geigy, 3(S)-[[(lS)-5-amino-l-carboxypentyl]amino]-2,3,4,- 5-tetrahydro-2-oxo-lH-l- benzazepine-1-ethanoic acid, see US4473575), Ru 44570 (Hoechst, see Arzneimittelforschung 34:1254 (1985)), R 31-2201 (Hoffman-LaRoche see FEBS Lett. 165:201 (1984)), CI925 (Pharmacologist 26:243, 266 (1984)), WY-44221 (Wyeth, see J. Med. Chem. 26:394 (1983)), and those disclosed in

US2003006922 (paragraph 28), US4337201, US4432971 (phosphonamidates); neutral endopeptidase inhibitors such as omapatrilat (Vanlev®), CGS 30440, cadoxatril and ecadotril, fasidotril (also known as aladotril or alatriopril), sampatrilat, mixanpril, and gemopatrilat, AVE7688, ER4030, and those disclosed in US5362727, US5366973, US5225401, US4722810, US5223516, US4749688, US5552397, US5504080, US5612359, US5525723, EP0599444, EP0481522, EP0599444, EP0595610, EP0534363, EP534396, EP534492, EP0629627; endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; vasodilators such as hydralazine (apresoline), clonidine (clonidine hydrochloride (1H-Imidazol- 2-amine, N-(2,6-dichlorophenyl)4,5-dihydro-, monohydrochloride CAS RN 4205-91-8), catapres, minoxidil (loniten), nicotinyl alcohol (roniacol), diltiazem hydrochloride (such as 1,5- Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4- methoxyphenyl)-, monohydrochloride, (+)-cis, e.g., Tiazac®, Forest), isosorbide dinitrate (such as l,4:3,6-dianhydro-D-glucitol 2,5-dinitrate e.g., Isordil® Titradose®, Wyeth- Ayerst), sosorbide mononitrate (such as l,4:3,6-dianhydro-D-glucito- 1,5-nitrate, an organic nitrate, e.g., Ismo®, Wyeth-Ayerst), nitroglycerin (such as 2,3 propanetriol trinitrate, e.g., Nitrostat® Parke- Davis), verapamil hydrochloride (such as benzeneacetonitrile, (±)-(alpha)[3-[[2-(3,4 dimethoxypheny l)ethyl]methylamino]propyl] -3 ,4-dimethoxy-(alpha)- (1 -methylethyl) hydrochloride, e.g., Covera HS® Extended-Release, Searle), chromonar (which may be prepared as disclosed in US3282938), clonitate (Annalen 1870 155), droprenilamine (which may be prepared as disclosed in DE2521113), lidoflazine (which may be prepared as disclosed in US3267104); prenylamine (which may be prepared as disclosed in US3152173), propatyl nitrate (which may be prepared as disclosed in French Patent No. 1,103,113), mioflazine hydrochloride (1 -Piperazineacetamide, 3-(aminocarbonyl)4-[4,4-bis(4-fluorophenyl)butyl]-N-(2,6- dichlorophenyl)-, dihydrochloride CAS RN 83898-67-3), mixidine (Benzeneethanamine, 3,4- dimethoxy-N-(l-methyl-2-pyrrolidinylidene)- Pyrrolidine, 2-[(3,4-dimethoxyphenethyl)imino]- 1 -methyl- l-Methyl-2- [(3, 4-dimethoxyphenethyl)imino]pyrrolidine CAS RN 27737-38-8), molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), isosorbide mononitrate (D-Glucitol, l,4:3,6-dianhydro-, 5-nitrate CAS RN 16051-77-7), erythrityl tetranitrate (1,2,3,4-Butanetetrol, tetranitrate, (2R,3S)-rel-CAS RN 7297-25-8), clonitrate(l,2-Propanediol, 3-chloro-, dinitrate (7CI, 8CI, 9CI) CAS RN 2612-33-1), dipyridamole Ethanol, 2,2',2",2'"-[(4,8-di-l-piperidinylpyrimido[5,4-d]pyrimidine-2,6-

diyl)dinitrilo]tetrakis- CAS RN 58-32-2), nicorandil (CAS RN 65141-46-0 3-), pyridinecarboxamide (N-[2-(nitrooxy)ethyl]-Nisoldipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester CAS RN 63675-72-9), nifedipine3,5-Pyridinedicarboxylic acid, l,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester CAS RN 21829-25-4), perhexiline maleate (Piperidine, 2-(2,2-dicyclohexylethyl)-, (2Z)-2-butenedioate (1 :1) CAS RN 6724-53-4), oxprenolol hydrochloride (2-Propanol, 1-[(1-methylethyl)amino]-3-[2-(2-propenyloxy)phenoxy]-, hydrochloride CAS RN 6452-73-9), pentrinitrol (1,3-Propanediol, 2,2-bis[(nitrooxy)methyl]-, mononitrate (ester) CAS RN 1607-17-6), verapamil (Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]- methylamino]propyl]-3, 4-dimethoxy-α-(l -methylethyl)- CAS RN 52-53-9) and the like; angiotensin II receptor antagonists such as, aprosartan, zolasartan, olmesartan, pratosartan, FI6828K, RNH6270, candesartan (1 H-Benzimidazole-7-carboxylic acid, 2-ethoxy-l-[[2'-(lH-tetrazol-5-yl)[l,l'-biphenyl]4-yl]methyl]- CAS RN 139481-59-7), candesartan cilexetil ((+/-)-l-(cyclohexylcarbonyloxy)ethyl-2-ethoxy-l-[[2'-(lH-tetrazol-5-yl)biphenyl-4-yl]-lH-benzimidazole carboxylate, CAS RN 145040-37-5, US5703110 and US5196444), eprosartan (3-[l-4-carboxyphenylmethyl)-2-n-butyl-imidazol-5-yl]-(2-thienylmethyl) propenoic acid, US5185351 and US5650650), irbesartan (2-n-butyl-3- [[2'-(lh-tetrazol-5-yl)biphenyl-4-yl]methyl] 1 ,3-diazazspiro[4,4]non-l-en-4-one, US5270317 and US5352788), losartan (2-N-butyl-4-chloro-5-hydroxymethyl-l-[(2'-(lH-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole, potassium salt, US5138069, US5153197 and US5128355), tasosartan (5,8-dihydro-2,4-dimethyl-8-[(2'-(lH-tetrazol-5-yl)[l,r-biphenyl]4-yl)methyl]-pyrido[2,3-d]pyrimidin-7(6H)-one, US5149699), telmisartan (4'-[(1 ,4-dimethyl-2'-propyl-(2,6'-bi-lH-benzimidazol)-r-yl)]-[1 , 1 '-biphenyl]-2-carboxylic acid, CAS RN 144701-48-4, US5591762), milfasartan, abitesartan, valsartan (Diovan® (Novartis), (S)-N-valeryl-N-[[2'-(lH-tetrazol-5-yl)biphenyl-4-yl)methyl]valine, US5399578), EXP-3137 (2-N-butyl-4-chloro-l-[(2'-(lH-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole-5-carboxylic acid, US5138069, US5153197 and US5128355), 3-(2'-(tetrazol-5-yl)-l,r-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, 4'[2-ethyl-4-methyl-6-(5,6,7,8-tetrahydroimidazo[l,2-a]pyridin-2-yl]-benzimidazol-l-yl]-methyl]-l,r-biphenyl]-2- carboxylic acid, 2-butyl-6-(l-methoxy-l-methylethyl)-2-[2'-)IH-tetrazol-5-yl)biphenyl-4-ylmethyl] guinazolin-4(3H)-one, 3 - [2 ' -carboxybiphenyl-4-yl)methyl] -2-cyclopropyl-7-methyl- 3H-imidazo[4,5-b]pyridine, 2-butyl-4-chloro-l-[(2'-tetrazol-5-

yl)biphenyl-4-yl)methyl]imidazole-carboxylic acid, 2-butyl-4-chloro-l-[[2'-(lH-tetrazol-5- yl) [1 , 1 ' -biphenyl] -4-yl]methyl]- 1 H-imidazole-5 -carboxylic acid- 1 -(ethoxycarbonyl-oxy)ethyl ester potassium salt, dipotassium 2-butyl-4-(methylthio)-l-[[2-[[[(propylamino)carbonyl]amino]-sulfonyl](l,l '-biphenyl)-4-yl]methyl]-l H-imidazole-5 -carboxylate, methyl-2-[[4-butyl-2-methyl-6-oxo-5-[[2'-(lH-tetrazol-5-yl)-[l,l '-biphenyl]-4-yl]methyl]-l-(6H)- pyrimidinyl]methyl]-3-thiophencarboxylate, 5-[(3,5-dibutyl-lH-l,2,4-triazol-l-yl)methyl]-2-[2- (1 H-tetrazol-5 -ylphenyl)]pyridine, 6-butyl-2-(2-phenylethyl)-5 [[2'-(I H-tetrazol-5 -yl)[1,1 '- biphenyl]-4-methyl]pyrimidin-4-(3H)-one D,L lysine salt, 5-methyl-7-n-propyl-8-[[2'-(lH- tetrazol-5-yl)biphenyl-4-yl]methyl]-[1 ,2,4]-triazolo[1 ,5-c]pyrimidin-2(3H)-one, 2,7-diethyl-5- [[2'-(5-tetrazoly)biphenyl-4-yl]methyl]-5H-pyrazolo[l,5-b][l,2,4]triazole potassium salt, 2-[2- butyl-4,5-dihydro-4-oxo-3-[2'-(lH-tetrazol-5-yl)-4-biphenylmethyl]-3H-imidazol[4,5- c]pyridine-5-ylmethyl]benzoic acid, ethyl ester, potassium salt, 3-methoxy-2,6-dimethyl-4- [[2'(lH-tetrazol-5-yl)-l,l '-biphenyl-4-yl]methoxy]pyridine, 2-ethoxy-l-[[2'-(5-oxo-2,5-dihydro- 1 ,2,4-oxadiazol-3 -yl)biphenyl-4-yl]methyl] - 1 H-benzimidazole-7-carboxylic acid, 1 - [N-(2 ' -(1 H- tetrazol-5-yl)biphenyl-4-yl-methyl)-N-valerolylaminomethyl)cyclopentane- 1 -carboxylic acid, 7- methyl-2n-propyl-3-[[2' lH-tetrazol-5-yl)biphenyl-4-yl]methyl]-3H-imidazo[4,5-6]pyridine, 2- [5-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine-3-yl)methyl]-2-quinolinyl]sodium benzoate, 2-butyl-6-chloro-4-hydroxymethyl-5 -methyl-3 -[[2'-(I H-tetrazol-5 -yl)biphenyl-4-yl]methyl]pyridine, 2- [[[2-butyl- 1 - [(4-carboxyphenyl)methyl] - 1 H-imidazol-5 -yl]methyl]amino]benzoic acid tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-6-one, 4(S)- [4-(carboxymethyl)phenoxy]-N-[2(R)-[4-(2-sulfobenzamido)imidazol- 1 -yl]octanoyl]-L-proline, 1 - (2,6-dimethylphenyl)-4-butyl-l,3-dihydro-3-[[6-[2-(lH-tetrazol-5-yl)phenyl]-3-pyridinyl]methyl]-2H-imidazol-2-one, 5 ,8-ethano-5 ,8-dimethyl-2-n-propyl-5 ,6,7,8-tetrahydro-1 - [[2'(lH-tetrazol-5-yl)biphenyl-4-yl]methyl]-lH,4H-l,3,4a,8a-tetrazacyclopentanaphthalene-9-one, 4-[l-[2'-(l,2,3,4-tetrazol-5-yl)biphen-4-yl)methylamino]-5,6,7,8-tetrahydro-2-trifylquinazoline, 2-(2-chlorobenzoyl)imino-5-ethyl-3-[2'-(lH-tetrazole-5-yl)biphenyl-4-yl)methyl-l,3,4-thiadiazoline, 2-[5-ethyl-3-[2-(lH-tetrazole-5-yl)biphenyl-4-yl]methyl-l,3,4-thiazoline-2-ylidene]aminocarbonyl-l-cyclopentencarboxylic acid dipotassium salt, and 2-butyl-4-[N-methyl-N-(3 -methylcrotonoyl)amino] - 1 - [[2 ' -(1 H-tetrazol-5 -yl)biphenyl-4-yl]methyl]- 1 H- imidzole-5 -carboxylic acid 1-ethoxycarbonyloxyethyl ester, those disclosed in patent publications EP475206, EP497150, EP539086, EP539713, EP535463, EP535465,

EP542059, EP497121, EP535420, EP407342, EP415886, EP424317, EP435827, EP433983, EP475898, EP490820, EP528762, EP324377, EP323841, EP420237, EP500297, EP426021, EP480204, EP429257, EP430709, EP434249, EP446062, EP505954, EP524217, EP514197, EP514198, EP514193, EP514192, EP450566, EP468372, EP485929, EP503162, EP533058, EP467207 EP399731, EP399732, EP412848, EP453210, EP456442, EP470794, EP470795, EP495626, EP495627, EP499414, EP499416, EP499415, EP511791, EP516392, EP520723, EP520724, EP539066, EP438869, EP505893, EP530702, EP400835, EP400974, EP401030, EP407102, EP411766, EP409332, EP412594, EP419048, EP480659, EP481614, EP490587, EP467715, EP479479, EP502725, EP503838, EP505098, EP505111 EP513,979 EP507594, EP510812, EP511767, EP512675, EP512676, EP512870, EP517357, EP537937, EP534706, EP527534, EP540356, EP461040, EP540039, EP465368, EP498723, EP498722, EP498721, EP515265, EP503785, EP501892, EP519831, EP532410, EP498361, EP432737, EP504888, EP508393, EP508445, EP403159, EP403158, EP425211, EP427463, EP437103, EP481448, EP488532, EP501269, EP500409, EP540400, EP005528, EP028834, EP028833, EP411507, EP425921, EP430300, EP434038, EP442473, EP443568, EP445811, EP459136, EP483683, EP518033, EP520423, EP531876, EP531874, EP392317, EP468470, EP470543, EP502314, EP529253, EP543263, EP540209, EP449699, EP465323, EP521768, EP415594, WO92/14468, WO93/08171, WO93/08169, WO91/00277, WO91/00281, WO91/14367, WO92/00067, WO92/00977, WO92/20342, WO93/04045, WO93/04046, WO91/15206, WO92/14714, WO92/09600, WO92/16552, WO93/05025, WO93/03018, WO91/07404, WO92/02508, WO92/13853, WO91/19697, WO91/11909, WO91/12001, WO91/11999, WO91/15209, WO91/15479, WO92/20687, WO92/20662, WO92/20661, WO93/01177, WO91/14679, WO91/13063, WO92/13564, WO91/17148, WO91/18888, WO91/19715, WO92/02257, WO92/04335, WO92/05161, WO92/07852, WO92/15577, WO93/03033, WO91/16313, WO92/00068, WO92/02510, WO92/09278, WO9210179, WO92/10180, WO92/10186, WO92/10181, WO92/10097, WO92/10183, WO92/10182, WO92/10187, WO92/10184, WO92/10188, WO92/10180, WO92/10185, WO92/20651, WO93/03722, WO93/06828, WO93/03040, WO92/19211, WO92/22533, WO92/06081, WO92/05784, WO93/00341, WO92/04343, WO92/04059, US5104877, US5187168, US5149699, US5185340, US4880804, US5138069, US4916129, US5153197, US5173494, US5137906, US5155126, US5140037, US5137902, US5157026, US5053329, US5132216, US5057522, US5066586, US5089626,

US5049565, US5087702, US5124335, US5102880, US5128327, US5151435, US5202322, US5187159, US5198438, US5182288, US5036048, US5140036, US5087634, US5196537, US5153347, US5191086, US5190942, US5177097, US5212177, US5208234, US5208235, US5212195, US5130439, US5045540, US5041152, and US5210204, and pharmaceutically acceptable salts and esters thereof; α/β adrenergic blockers such as nipradilol, arotinolol, amosulalol, bretylium tosylate (CAS RN: 61-75-6), dihydroergtamine mesylate (such as ergotaman-3', 6',18-trione,9,-10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-,(5'(α))-, monomethanesulfonate, e.g., DHE 45® Injection, Novartis), carvedilol (such as (±)-l-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl] amino] -2-propanol, e.g., Coreg®, SmithKline Beecham), labetalol (such as 5-[l-hydroxy-2-[(l-methyl-3-phenylpropyl) amino] ethyljsalicylamide monohydrochloride, e.g., Normodyne®, Schering), bretylium tosylate (Benzenemethanaminium, 2-bromo-N-ethyl-N,N-dimethyl-, salt with 4-methylbenzenesulfonic acid (1 :1) CAS RN 61-75-6), phentolamine mesylate (Phenol, 3-[[(4,5-dihydro-lH-imidazol-2-yl)methyl](4-methylphenyl)amino]-, monomethanesulfonate (salt) CAS RN 65-28-1), solypertine tartrate (5H-l,3-Dioxolo[4,5-f]indole, 7-[2-[4-(2-methoxyphenyl)-l-piperazinyl]ethyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1 :1) CAS RN 5591-43-5), zolertine hydrochloride (Piperazine, l-phenyl4-[2-(lH-tetrazol-5-yl)ethyl]-, monohydrochloride (8Cl, 9Cl) CAS RN 7241-94-3) and the like; α adrenergic receptor blockers, such as alfuzosin (CAS RN: 81403-68-1), terazosin, urapidil, prazosin (Minipress®), tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, XENOlO, fenspiride hydrochloride (which may be prepared as disclosed in US3399192), proroxan (CAS RN 33743-96-3), and labetalol hydrochloride and combinations thereof; α 2 agonists such as methyldopa, methyldopa HCL, lofexidine, tiamenidine, moxonidine, rilmenidine, guanobenz, and the like; aldosterone inhibitors, and the like; renin inhibitors including Aliskiren (SPPlOO; Novartis/Speedel); angiopoietin-2-binding agents such as those disclosed in WO03/030833; anti-angina agents such as ranolazine (hydrochloride 1-Piperazineacetamide, N-(2,6- dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635- 56-6), betaxolol hydrochloride (2-Propanol, l-[4-[2 (cyclopropylmethoxy)ethyl]phenoxy]-3-[(l- methylethyl)amino]-, hydrochloride CAS RN 63659-19-8), butoprozine hydrochloride (Methanone, [4-[3(dibutylamino)propoxy]phenyl](2-ethyl-3-indolizinyl)-, monohydrochloride CAS RN 62134-34-3), cinepazet maleatel-Piperazineacetic acid, 4-[l-oxo-3-(3,4,5- trimethoxyphenyl)-2-

propenyl]-, ethyl ester, (2Z)-2-butenedioate (1 :1) CAS RN 50679-07-7), tosifen (Benzenesulfonamide, 4-methyl-N-[[[(lS)-l-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184), verapamilhydrochloride (Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3 ,4-dimethoxy-α-(1 -methylethyl)-, monohydrochloride CAS RN 152-114), molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), and ranolazine hydrochloride (1 -Piperazineacetamide, N-(2,6-dimethylphenyl)4-[2-hydroxy-3-(2-meth-oxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6); tosifen (Benzenesulfonamide, 4-methyl-N-[[[(lS)-l-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184); adrenergic stimulants such as guanfacine hydrochloride (such as N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride, e.g., Tenex® Tablets available from Robins); methyldopa-hydrochlorothiazide (such as levo-3-(3,4-dihydroxyphenyl)-2-methylalanine) combined with Hydrochlorothiazide (such as 6-chloro-3,4-dihydro-2H -l,2,4-benzothiadiazine-7- sulfonamide 1,1-dioxide, e.g., the combination as, e.g., Aldoril® Tablets available from Merck), methyldopa-chlorothiazide (such as 6-chloro-2H-l, 2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and methyldopa as described above, e.g., Aldoclor®, Merck), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride and chlorthalidone (such as 2-chloro-5-(l-hydroxy-3-oxo-l-isoindolinyl) benzenesulfonamide), e.g., Combipres®, Boehringer Ingelheim), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride, e.g., Catapres®, Boehringer Ingelheim), clonidine (lH-Imidazol-2-amine, N-(2,6-dichlorophenyl)4,5-dihydro-CAS RN 4205-90-7), Hyzaar (Merck; a combination of losartan and hydrochlorothiazide), Co-Diovan (Novartis; a combination of valsartan and hydrochlorothiazide, Lotrel (Novartis; a combination of benazepril and amlodipine) and Caduet (Pfizer; a combination of amlodipine and atorvastatin), and those agents disclosed in US20030069221.

1.3.2.11 Agents for the Treatment of Respiratory Disorders

[173] The GCC agonist peptides described herein can be used in combination therapy with one or more of the following agents useful in the treatment of respiratory and other disorders including but not limited to: (1) β-agonists including but not limited to : albuterol (PRO VENTIL® , S ALBUT AMOl® , VENTOLIN®), bambuterol, bitoterol, clenbuterol, fenoterol,

formoterol, isoetharine (BRONKOSOL®, BRONKOMETER®), metaproterenol (ALUPENT®, METAPREL®), pirbuterol (MAXAIR®), reproterol, rimiterol, salmeterol, terbutaline (BRETHAIRE®, BRETHINE®, BRICANYL®), adrenalin, isoproterenol (ISUPREL®), epinephrine bitartrate (PRIMATENE®), ephedrine, orciprenline, fenoterol and isoetharine; (2) steroids, including but not limited to beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, bunedoside, butixocort, dexamethasone, flunisolide, fluocortin, fluticasone, hydrocortisone, methyl prednisone, mometasone, predonisolone, predonisone, tipredane, tixocortal, triamcinolone, and triamcinolone acetonide; (3) β2-agonist-corticosteroid combinations [e.g., salmeterol-fluticasone (AD V AIR®), formoterol-budesonid (S YMBICORT®)] ; (4) leukotriene D4 receptor antagonists/leukotriene antagonists/LTD4 antagonists (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between leukotrienes and the Cys LTI receptor) including but not limited to: zafhiukast, montelukast, montelukast sodium (SINGULAIR®), pranlukast, iralukast, pobilukast, SKB-106,203 and compounds described as having LTD4 antagonizing activity described in U.S. Patent No. 5,565,473; (5) 5 -lipoxygenase inhibitors and/or leukotriene biosynthesis inhibitors [e.g., zileuton and BAY1005 (CA registry 128253-31-6)]; (6) histamine Hl receptor antagonists/antihistamines (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between histamine and its receptor) including but not limited to: astemizole, acrivastine, antazoline, azatadine, azelastine, astamizole, bromopheniramine, bromopheniramine maleate, carbinoxamine, carebastine, cetirizine, chlorpheniramine, chloropheniramine maleate, cimetidine clemastine, cyclizine, cyproheptadine, descarboethoxyloratadine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine succinate, doxylarnine, ebastine, efletirizine, epinastine, famotidine, fexofenadine, hydroxyzine, hydroxyzine, ketotifen, levocabastine, levocetirizine, levocetirizine, loratadine, meclizine, mepyramine, mequitazine, methdilazine, mianserin, mizolastine, noberastine, norasternizole, noraztemizole, phenindamine, pheniramine, picumast, promethazine, pynlamine, pyrilamine, ranitidine, temelastine, terfenadine, trimeprazine, tripelenamine, and triprolidine; (7) an anticholinergic including but not limited to: atropine, benztropine, biperiden, flutropium, hyoscyamine (e.g. Levsin®; Levbid®; Levsin/SL®, Anaspaz®, Levsinex timecaps®, NuLev®), ilutropium, ipratropium, ipratropium bromide, methscopolamine, oxybutinin, rispenzepine, scopolamine, and tiotropium; (8) an anti-tussive

including but not limited to: dextromethorphan, codeine, and hydromorphone; (9) a decongestant including but not limited to: pseudoephedrine and phenylpropanolamine; (10) an expectorant including but not limited to: guafenesin, guaicolsulfate, terpin, ammonium chloride, glycerol guaicolate, and iodinated glycerol; (11) a bronchodilator including but not limited to: theophylline and aminophylline; (12) an anti-inflammatory including but not limited to: fluribiprofen, diclophenac, indomethacin, ketoprofen, S-ketroprophen, tenoxicam; (13) a PDE (phosphodiesterase) inhibitor including but not limited to those disclosed herein; (14) a recombinant humanized monoclonal antibody [e.g. xolair (also called omalizumab), rhuMab, and talizumab]; (15) a humanized lung surfactant including recombinant forms of surfactant proteins SP-B, SP-C or SP-D [e.g. SURFAXIN®, formerly known as dsc-104 (Discovery Laboratories)], (16) agents that inhibit epithelial sodium channels (ENaC) such as amiloride and related compounds; (17) antimicrobial agents used to treat pulmonary infections such as acyclovir, amikacin, amoxicillin, doxycycline, trimethoprin sulfamethoxazole, amphotericin B, azithromycin, clarithromycin, roxithromycin, clarithromycin, cephalosporins(ceffoxitin, cefmetazole etc), ciprofloxacin, ethambutol, gentimycin, ganciclovir, imipenem, isoniazid, itraconazole, penicillin, ribavirin, rifampin, rifabutin,amantadine, rimantidine, streptomycin, tobramycin, and vancomycin; (18) agents that activate chloride secretion through Ca++ dependent chloride channels (such as purinergic receptor (P2Y(2) agonists); (19) agents that decrease sputum viscosity, such as human recombinant DNase 1, (Pulmozyme®); (20) nonsteroidal anti-inflammatory agents (acemetacin, acetaminophen, acetyl salicylic acid, alclofenac, alminoprofen, apazone, aspirin, benoxaprofen, bezpiperylon, bucloxic acid, carprofen, clidanac, diclofenac, diclofenac, diflunisal, diflusinal, etodolac, fenbufen, fenbufen, fenclofenac, fenclozic acid, fenoprofen, fentiazac, feprazone, flufenamic acid, flufenisal, flufenisal, fluprofen, flurbiprofen, flurbiprofen, furofenac, ibufenac, ibuprofen, indomethacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketoprofen, ketorolac, meclofenamic acid, meclofenamic acid, mefenamic acid, mefenamic acid, miroprofen, mofebutazone, nabumetone oxaprozin, naproxen, naproxen, niflumic acid , oxaprozin, oxpinac, oxyphenbutazone, phenacetin, phenylbutazone, phenylbutazone, piroxicam, piroxicam, pirprofen, pranoprofen, sudoxicam, tenoxican, sulfasalazine, sulindac, sulindac, suprofen, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, tolmetin, zidometacin,

zomepirac, and zomepirac); and (21) aerosolized antioxidant therapeutics such as S-Nitrosoglutathione.

1.3.2.12 Anti-Diabetic Agents

[174] The GCC agonist peptides described herein can be used in therapeutic combination with one or more anti-diabetic agents, including but not limited to: PPARγ agonists such as glitazones (e.g., WAY-120,744, AD 5075, balaglitazone, ciglitazone, darglitazone (CP-86325, Pfizer), englitazone (CP-68722, Pfizer), isaglitazone (MIT/J&J), MCC- 555 (Mitsibishi disclosed in US5594016), pioglitazone (such as such as Actos™ pioglitazone; Takeda), rosiglitazone (Avandia™;Smith Kline Beecham), rosiglitazone maleate, troglitazone (Rezulin®, disclosed in US4572912), rivoglitazone (CS-Ol 1, Sankyo), GL-262570 (Glaxo Welcome), BRL49653 (disclosed in WO98/05331), CLX-0921, 5-BTZD, GW-0207, LG- 100641, JJT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/Pfizer), NN-2344 (Dr. Reddy/NN), YM-440 (Yamanouchi), LY-300512, LY-519818, R483 (Roche), T131 (Tularik), and the like and compounds disclosed in US4687777, US5002953, US5741803, US5965584, US6150383, US6150384, US6166042, US6166043, US6172090, US6211205, US6271243, US6288095, US6303640, US6329404, US5994554, W097/10813, WO97/27857, WO97/28115, WO97/28137,WO97/27847, WO00/76488, WO03/000685,WO03/027112,WO03/035602, WO03/048130, WO03/055867, and pharmaceutically acceptable salts thereof; biguanides such as metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride, such as Glucophage™, Bristol-Myers Squibb); metformin hydrochloride with glyburide, such as Glucovance™, Bristol-Myers Squibb); buformin (Imidodicarbonimidic diamide, N-butyl-); etoformine (l-Butyl-2-ethylbiguanide, Schering A. G.); other metformin salt forms (including where the salt is chosen from the group of, acetate, benzoate, citrate, ftimarate, embonate, chlorophenoxyacetate, glycolate, palmoate, aspartate, methanesulphonate, maleate, parachlorophenoxyisobutyrate, formate, lactate, succinate, sulphate, tartrate, cyclohexanecarboxylate, hexanoate, octanoate, decanoate, hexadecanoate, octodecanoate, benzenesulphonate, trimethoxybenzoate, paratoluenesulphonate, adamantanecarboxylate, glycoxylate, glutarnate, pyrrolidonecarboxylate, naphthalenesulphonate, 1-glucosephosphate, nitrate, sulphite, dithionate and phosphate), and phenformin; protein tyrosine phosphatase- IB

(PTP-IB) inhibitors, such as A-401,674, KR 61639, OC- 060062, OC-83839, OC-297962, MC52445, MC52453, ISIS 113715, and those disclosed in WO99/585521, WO99/58518, WO99/58522, WO99/61435, WO03/032916, WO03/032982, WO03/041729, WO03/055883, WO02/26707, WO02/26743, JP2002114768, and pharmaceutically acceptable salts and esters thereof; sulfonylureas such as acetohexamide (e.g. Dymelor, Eli Lilly), carbutamide, chlorpropamide (e.g. Diabinese®, Pfizer), gliamilide (Pfizer), gliclazide (e.g. Diamcron, Servier Canada Inc), glimepiride (e.g. disclosed in US4379785, such as Amaryl , Aventis), glipentide, glipizide (e.g. Glucotrol or Glucotrol XL Extended Release, Pfizer), gliquidone, glisolamide, glyburide/glibenclamide (e.g. Micronase or Glynase Prestab, Pharmacia & Upjohn and Diabeta, Aventis), tolazamide (e.g. Tolinase), and tolbutamide (e.g. Orinase), and pharmaceutically acceptable salts and esters thereof; meglitinides such as repaglinide (e.g. Pranidin®, Novo Nordisk), KAD1229 (PF/Kissei), and nateglinide (e.g. Starlix®, Novartis), and pharmaceutically acceptable salts and esters thereof; α glucoside hydrolase inhibitors (or glucoside inhibitors) such as acarbose (e.g. Precose™, Bayer disclosed in US4904769), miglitol (such as GLYSET™, Pharmacia & Upjohn disclosed in US4639436), camiglibose (Methyl 6-deoxy-6-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2- (hydroxymethyl)piperidino]-alpha-D-glucopyranoside, Marion Merrell Dow), voglibose (Takeda), adiposine, emiglitate, pradimicin-Q, salbostatin, CKD-711, MDL-25,637, MDL- 73,945, and MOR 14, and the compounds disclosed in US4062950, US4174439, US4254256, US4701559, US4639436, US5192772, US4634765, US5157116, US5504078, US5091418, US5217877, US51091 and WOO 1/47528 (polyamines); α-amylase inhibitors such as tendamistat, trestatin, and Al -3688, and the compounds disclosed in US4451455, US4623714, and US4273765; SGLT2 inhibtors including those disclosed in US6414126 and US6515117; an aP2 inhibitor such as disclosed in US6548529; insulin secreatagogues such as linogliride, A-4166, forskilin, dibutyrl cAMP, isobutylmethylxanthine (IBMX), and pharmaceutically acceptable salts and esters thereof; fatty acid oxidation inhibitors, such as clomoxir, and etomoxir, and pharmaceutically acceptable salts and esters thereof; A2 antagonists, such as midaglizole, isaglidole, deriglidole, idazoxan, earoxan, and fluparoxan, and pharmaceutically acceptable salts and esters thereof; insulin and related compounds (e.g. insulin mimetics) such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente), Lys-Pro insulin, GLP-I (1-36) amide, GLP-I (73-7) (insulintropin, disclosed in US5614492), LY-315902 (Lilly), GLP-I (7-36)-NH2), AL-401

(Autoimmune), certain compositions as disclosed in US4579730, US4849405, US4963526, US5642868, US5763396, US5824638, US5843866, US6153632, US6191105, and WO 85/05029, and primate, rodent, or rabbit insulin including biologically active variants thereof including allelic variants, more preferably human insulin available in recombinant form (sources of human insulin include pharmaceutically acceptable and sterile formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin™ (human insulin rDNA origin), also see the THE PHYSICIAN'S DESK REFERENCE, 55.sup.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins); non-thiazolidinediones such as JT-501 and farglitazar (GW-2570/GI- 262579), and pharmaceutically acceptable salts and esters thereof; PPARα/γ dual agonists such as AR-HO39242 (Aztrazeneca), GW-409544 (Glaxo-Wellcome), BVT-142, CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297 (Kyorin Merck; 5-[(2,4-Dioxo thiazolidinyl)methyl] methoxy-N-[[4-(trifluoromethyl)phenyl] methyljbenzamide), L-796449, LR-90, MK-0767 (Merck/Kyorin/Banyu), SB 219994, muraglitazar (BMS), tesaglitzar (Astrazeneca), reglitazar (JTT-501) and those disclosed in WO99/16758, WO99/19313, WO99/20614, WO99/38850, WO00/23415, WO00/23417, WO00/23445, WO00/50414, WO01/00579, WO01/79150, WO02/062799, WO03/004458, WO03/016265, WO03/018010, WO03/033481, WO03/033450, WO03/033453, WO03/043985, WO 031053976, U.S. application Ser. No. 09/664,598, filed Sep. 18, 2000, Murakami et al. Diabetes 47, 1841-1847 (1998), and pharmaceutically acceptable salts and esters thereof; other insulin sensitizing drugs; VPAC2 receptor agonists; GLK modulators, such as those disclosed in WO03/015774; retinoid modulators such as those disclosed in WO03/000249; GSK 3β/GSK 3 inhibitors such as 4-[2-(2-bromophenyl)-4-(4-fluorophenyl-lH-imidazol-5- yl]pyridine and those compounds disclosed in WO03/024447, WO03/037869, WO03/037877, WO03/037891, WO03/068773, EP1295884, EP1295885, and the like; glycogen phosphorylase (HGLPa) inhibitors such as CP-368,296, CP-316,819, BAYR3401, and compounds disclosed in WOO 1/94300, WO02/20530, WO03/037864, and pharmaceutically acceptable salts or esters thereof; ATP consumption promotors such as those disclosed in WO03/007990; TRB3 inhibitors; vanilloid receptor ligands such as those disclosed in WO03/049702; hypoglycemic agents such as those disclosed in WO03/015781 and WO03/040114; glycogen synthase kinase 3 inhibitors such as those disclosed in WO03/035663 agents such as those disclosed in WO99/51225, US20030134890, WO01/24786, and

WO03/059870; insulin-responsive DNA binding protein-1 (IRDBP-I) as disclosed in WO03/057827, and the like; adenosine A2 antagonists such as those disclosed in WO03/035639, WO03/035640, and the like; PPARδ agonists such as GW 501516, GW 590735, and compounds disclosed in JP10237049 and WO02/14291; dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, NVP-DPP728A (1- [[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999), P32/98, NVP-LAF-237, P3298, TSL225 (tryptophyl-l,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), valine pyrrolidide, TMC-2A/2B/2C, CD- 26 inhibitors, FE999011, P9310/K364, VIP 0177, DPP4, SDZ 274-444, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) ,and the compounds disclosed in US6395767, US6573287, US6395767 (compounds disclosed include BMS-477118, BMS-471211 and BMS 538,305), WO99/38501, WO99/46272, WO99/67279, WO99/67278, WO99/61431WO03/004498, WO03/004496, EP1258476, WO02/083128, WO02/062764, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/000180, and WO03/000181; GLP-I agonists such as exendin-3 and exendin-4 (including the 39 aa polypeptide synthetic exendin-4 called Exenatide®), and compounds disclosed in US2003087821 and NZ 504256, and pharmaceutically acceptable salts and esters thereof; peptides including amlintide and Symlin® (pramlintide acetate); and glycokinase activators such as those disclosed in US2002103199 (fused heteroaromatic compounds) and WO02/48106 (isoindolin-1-one-substituted propionamide compounds).

EXAMPLES

Example 1: Clinical Study for safety and efficacy in humans for the treatment of chronic idiopathic constipation

[175] A randomized, double-blind, placebo-controlled, 14-day repeat oral, dose ranging study was conducted in patients with chronic idiopathic constipation (CIC). The primary objective of this study was to evaluate the safety of SP-304 (1.0 mg, 3.0 mg, 9.0 mg and 0.3 mg) for 14 days in patients with CIC. One secondary objective was to assess the pharmacokinetic profile of

SP-304 in plasma. Other secondary objectives included evaluations of pharmacodynamic effects (efficacy) on parameters such as the time to first bowel movement after daily dosing with SP-304, bowel habits over time – for example, spontaneous bowel movements (SBMs), complete spontaneous bowel movements (CSBMs), and stool consistency [using Bristol Stool Form Scale (BSFS)] – and other patient reported outcomes such as abdominal discomfort.

[176] The study included five arms with assigned interventions as indicated in the table below.

Arms	Interventions
SP-304 1.0 mg: Experimental	Subjects receiving SP-304 1.0 mg for 14 consecutive days
SP-304 3.0 mg: Experimental	Subjects receiving SP-304 3.0 mg for 14 consecutive days
SP-304 9.0 mg: Experimental	Subjects receiving SP-304 9.0 mg for 14 consecutive days
Placebo: Placebo Comparator	Subjects receiving Placebo for 14 consecutive days
SP-304 0.3 mg: Experimental	Subjects receiving SP-304 0.3 mg for 14 consecutive days

[177] Subjects diagnosed with CIC were screened for the anticipated 4 cohorts to yield 80 randomized subjects for enrollment. There were four dose cohorts (1.0 mg, 3.0mg, 9.0 mg and 0.3 mg) with 20 subjects per dose cohort [randomization ratio 3:1 (15 receive SP-304:5 receive placebo)]. Subjects who continued to meet all the entry criteria and complete the pre-treatment bowel movement (BM) diary received, in a double-blind, randomized fashion, SP-304 or matching placebo. The entry criteria included (1) meeting modified ROME III criteria for chronic constipation (CC); (2) no significant finding in colonoscopy within past 5 years; (3) good health as determined by physical examination, medical history, vital signs, ECG, clinical chemistry, hematology, urinalysis, drug screen and serology assessments; and (4) during 14-day pre-treatment period, subjects reporting < 6 SBM and < 3 CSBM in each pre-treatment week. All subjects receiving at least one dose of SP-304 or matching placebo were considered evaluable for the safety endpoints (78 total). If a subject did not have a major protocol deviation, had at least 5 days of study treatment each week and corresponding entries for bowel habits, he/she was considered evaluable for efficacy parameters (54-55 total).

[178] The demographics of the subjects in the study are summarized in the table below.

	Placebo	0.3 mg	1.0 mg	3.0 mg	9.0 mg
			Age		
	47.7 (14.6)	51.1 (12.0)	50.5 (10.6)	48.5 (16.1)	47.3 (12.7)
			Gender		
Female	18 (90.0%)	12 (85.7%)	14 (100%)	13 (86.7)	12 (80%)
Male	2 (10.0%)	2 (14.3%)	0	2 (13.3%)	3 (20%)
			Race		
White	17 (85.0%)	13 (92.9%)	12 (85.7%)	14 (93.3%)	12 (80.0%)
African American	1 (5.0%)	0	1 (7.1%)	0	2 (13.3%)
Asian	1 (5.0%)	1 (7.1%)	1 (7.1%)	0	1 (6.7%)
American Indian	1 (5.0%)	0	0	0	0
Other	0	0	0	1 (6.7%)	0

Values for age are the mean (standard deviation); values for gender and race are the number (percentage of experimental arm).

Results

[179] Pharmacokinetics and Safety:

[180] There was no detectable systemic absorption of plecanatide (assay sensitivity $\geq$ 10 ng/mL). No serious adverse events (SAE) were reported in subjects receiving plecanatide and no deaths reported in this study. 10% (2/20) subjects who received placebo and 17.2% (10/58) subjects who received SP-304 reported adverse events considered as related to the treatment. The majority of adverse events were mild / moderate and transient in nature. 10% (2/20) subjects who received placebo and 5.2% (3/58) subjects who received SP-304 reported GI-related adverse events considered as related to treatment. There was no diarrhea reported for any subject receiving SP-304. The table below is a GI-related adverse event (AE) summary.

	Placebo n=20	0.3 mg n=14	1.0 mg n=14	3.0 mg n=15	9.0 mg n=15
Abdominal Cramping	1 (5.0%)	0	0	0	0
Abdominal Pain	1 (5.0%)	0	0	0	0
Bloating	0	0	0	0	1 (6.7%)
Diarrhea	1 (5.0%)	0	0	0	0
Flatulence	2 (10.0%)	0	0	0	0
Nausea	0	1 (7.1%)		0	0
Upset Stomach	0	0	0	1 (6.7%)	0

Values are the number (percentage of experimental arm).

[181] Efficacy:

[182] SP-304 (plecanatide) treatment decreased the time to first bowel movement, increased stool frequency (SBM and CSBM), improved stool consistency, and reduced straining and abdominal discomfort. See Figures 1-6.

Example 2: Composition of Wet Granulation batch 10005

Item No.	Ingredient	Use	Concentration % w/w
1	SP304		0.23
2	Mannogem EZ, USP/EP (Mannitol)	Diluent	79.77
3	PROSOLV SMCC 90 LM (silicified microcrystalline cellulose)	Binder	15.0
4	Purified Water (chilled to 5°C), USP	vehicle	n/a
5	Purified Water (chilled to 5°C), USP		n/a
6	Explotab (Sodium Starch Glycolate)	Disintregant	4.0

7	Pruv (sodium stearyl fumarate)	Lubricant	1.0
	Total		100

Example 3: Composition of Wet Granulation batch 10007

Item No.	Ingredient	Use	Concentration % w/w
1	SP304		0.3
3	PROSOLV SMCC 90 HD (silicified microcrystalline cellulose)	Binder	95.7
4	Purified Water (chilled to 5°C), USP	vehicle	n/a
5	Purified Water (chilled to 5°C), USP		n/a
6	Explotab (Sodium Starch Glycolate)	Disintregant	4.0
	Total		100

Example 4: EXCIPIENT COMPATIBILITY

[183] Binary mixtures of SP-304 were prepared and stored in glass vials. For solid excipients the binary mixtures were comprised of 9.1% or 50% excipient. Glass vials were stored at 40C/75RH open or closed. The percent purity (measured by HPLC) of the GCC agonist peptide (SP-304) after storage for the time indicated in each column (i.e., 1, 2, or 3 months for the closed vial and 0.5, 1, 2, or 3 months for the open vials) is indicated by numerical values.

		Closed			Open			
PURPOSE	EXCIPIENT	1M	2M	3M	0.5M	1M	2M	3M
None	None	91.4	88.2	84.1	93.7	91.2	88.2	84.8
Diluent	Sorbitol	92.4	90.1	87.2	92.2	90.8	87.1	80.9
	Mannitol	91.9	88.4	85.1	92.6	90.5	87.9	83.8
	Prosolv	92.2	89.6	86.3	93	90.5	87.8	83.7
	Starch	91.4	88.7	85.4	92.5	90.5	87.9	83.7
Binder	Emdex	91.3	88.7	85.2	91.8	90.7	87.9	81.9

	Plasdone	92.8	90.6	85.6	93.1	90.4	87.3	83
Disintegrant	Explotab	91.9	89.4	87.1	92.2	90.3	84.7	78.3
	Polyplasdone	92	89	85.6	93.5	90.3	87.4	83.1
Glidant	Cabosil	92.1	88.3	85.6	92.6	90.5	87.3	84
Lubricant	Mg stearte	91.5	87.7	84.6	92.6	90.6	87.6	83.8
	PRUV	92	88.3	85.7	92.2	90.5	87.5	83.8
	compritol	90.8	87.1	84.4	92	90.5	86.7	84.1
Excipient	PEG 3350	90.9	87	83.3	91.5	89.4	84.4	77.5
Antioxidant	Ascorbic acid	91.3	86.9	83	92.8	90	85.7	83.8
	BHA	91.9	88.9	85.9	93.5	90.8	87.4	85.8
	BHT	90.8	87.2	84.6	92.4	90.3	86.6	83.6
	EDTA	90.9	87.5	84.1	92.3	90.4	86.7	84.6
Capsule	HPMC capsule	92.2	89	85.2	92.3	90.2	86.4	83.5
	Gelatin capsule	91.5	88.3	84.3	84.3	90.5	86.7	83.6
Liquid for liquid filled capsule	Medium chain trig		90.4					
	PG dicaprylocaprate		89.3					
	Vit E		90					
	Soybean oil		89.6					
	Cremaphor		79.7					
	PG		3.4					
	PG 400		0.7					

Example 5: Geometric dry mix for 0.3mg capsule

[184] Place 12g mannitol in mortar. Add 4g SP-304 and gently mix until a visually uniform powder is obtained. Transfer to Turbula mixer. Rinse mortar with mannitol and transfer to Turbula mixer and mix at high speed for 10 minutes. Add about 150g of mannitol to 4 quart V-shell mixer. Transfer the contents of the Turbula mixer to the V-shell and add 150g of mannitol mix. Discharge v-shell contents and screen through 40 mesh and return to mixer. Add 586g of mannitol to mixer and mix for 20 minutes.

Example 6: Wet granulation process:

[185] Batch 017-10005 comprised of mannitol and low-moisture (2.4%) PROSOLV LM90 (0.33 g/mL) was sprayed with SP-304 solution and fluid bed dried resulted in granulation water content of 0.35%. The final blend contained 1% water, flowed well, and filled capsules well. The 2nd prototype 017-1006 comprised of the same components was adjusted to obtain a target capsule fill weight of 100 mg based on the results of the 1st batch. Water was sprayed onto powder blend with SP-304. The inlet temperature was 50C and the granulation was dried for 1.5 hours and stopped when the product temperature reached 36C. The 3rd (batch017-10006) and 4th (batch 017-10007) capsule prototypes will use PROSOLV HD90, which is a higher density material with superior flow properties and higher moisture content of 5.5% than the PROSOLV LM90. The moisture content of the PROSOLV HD90 is readily removed by fluid bed drying. The density of PROSOLV HD90 is about 0.55 g/mL. The PRUV lubricant will be removed for these batches.

Example 7: Wet granulation stability

[186] SP-304 was extracted from the capsules by sonication at either at room temperature (RT) or cold temperature and the amount of peptide was determined by HPLC. Initial percentages are based on the amount stated on the label.

Batch	% peptide (initial)	% peptide (1 mos at RT)
017-10006	101.1 (sonicated RT)	97.6 (sonicated cold)
017-10008	97.5 (sonicated RT)	108.2 (sonciated cold)

Example 8: 1M capsule stability in HDPE Bottles

[187] Capsules contained 0.3 mg SP-304 with the remainder of the fill weight (up to 5 mg) made up by mannitol (Perlitol 300 DC). Each capsule contained 1.5% by weight SP-304 and 98.5% mannitol. The capsule shell was composed of HPMC. Amounts are relative to the amount specified on the label (i.e., 0.30 mg peptide). The indicated number of capsules was placed in a high density polyethylene bottle with an induction seal and molecular sieve desiccant for 1 month at either 2-8C (first two columns) or 25C and 60% relative humidity (last two columns). The initial amount of peptide present was 101% of the label claim. The last row gives

the amount of peptide remaining after 1 month storage at the indicated temperature as determined by HPLC.

2-8C	2-8C	25C/60RH	25C/60RH
1-capsule per bottle	6-capsules per bottle	1-capsule per bottle	6-capsules per bottle
100%	92%	92%	98%

Example 9: Composition of batch 1528-2855-RD (capsules) and spray coating and drying process

Item No.	Ingredient	Amount per unit (mg)	Concentration % w/w
1	SP-304	0.3246	0.3246
2	Microcrystalline cellulose (Celphere SCP-100)	99.10	99.10
3	Calcium chloride dihydrate	0.2622	0.2622
4	Leucine USP	0.1171	0.1171
5	Hypromellose (Methocel E5 PremLV)	0.2000	0.2000
6	Purified Water, USP	7.2 mL*	n/a
	Total	100	100

*: The amount of water is calculated based on use of 119.0 mL purified water for the whole batch containing 5.356 g SP-304.

[188] The spray drying process of making the batch 2855-RD is described below.

Preparation of Coating Dispersion:

[189] Purified water was added to a glass container and stirred such that a liquid vortex was produced without introducing air. Then calcium chloride dihydrate was slowly added into the water. The mixture was stirred until the salt was dissolved or well dispersed. Next, leucine was slowly added and the resulting mixture was stirred until the amino acid was dissolved or well

dispersed. Afterward, methocel was slowly added and the mixture was stirred until methocel was completely dissolved. The solution could be warmed up to dissolve methocel, if necessary. The resulting excipient solution was allowed to cool to room temperature and pass through 80 mesh screen. Then, 127.9g of screened excipient solution was added to a glass container and placed in an ice bath for 0.5 to 1 hour until the solution reached 0 °C. Next, SP-304 was added into the cold excipient solution. The mixture was stir vigorously to allow the peptide to dissolve in the cold solution. The resulting peptide solution was kept cold in the ice bath as a spraying/coating solution.

Drug Layering

[190] A Glatt GPCG-2 fluid bed processor (with top spray tower) with a Wurster insert was set up for drug layering onto Celphere SCP-100 beads. After loading the Wurster column with Celphere SCP-100 beads, bed temperature was raised to 35 °C and maintained for 30 minutes with minimum fluidization of the beads. The bed temperature was reduced until an exhaust temperature of 35 °C was achieved. The pump tubing of the peristaltic pump used was primed by circulating the spraying solution mentioned above. After the spraying apparatus was adjusted to obtain a satisfactory spray pattern, the coating solution was sprayed onto Celphere SCP-100 beads until all coating solution was sprayed. Operating parameters were recorded. The bed temperature and fluidization were maintained until the beads were sufficiently dry. The fluidization was then reduced while the bed temperature was maintained at 35 °C for 10 minutes. 2g of beads were sampled for moisture analysis when the bed temperature was kept at 35 °C. When the moisture of the sampled beads reached < 5% moisture, the coated beads were discharged and loaded into a dry container. LOD (loss on drying) 2.399%.

Example 10: Composition of batch 1528-2851-RD (tablets) and spray coating and drying process

Item No.	Ingredient	Amount per unit (mg)	Concentration % w/w
1	SP-304	0.3246	0.3607
2	Microcrystalline	88.88	98.75

	cellulose (Avicel PH 102)		
3	Calcium chloride dihydrate	0.2622	0.2913
4	Leucine USP	0.1171	0.1301
5	Hypromellose (Methocel E5 PremLV)	0.2000	0.2222
6	Magnesium stearate	0.225	0.2500
7	Purified Water, USP	7.2 mL*	n/a
	Total	90.0	100

*: The amount of water is calculated based on use of 119.0 mL purified water for the whole batch containing 5.356 g SP-304.

[191] The spray coating and drying process of making the batch 2851-RD is described below.

Preparation of Coating Dispersion:

[192] Purified water was added to a glass container and stirred such that a liquid vortex was produced without introducing air. Then calcium chloride dihydrate was slowly added into the water. The mixture was stirred until the salt was dissolved or well dispersed. Next, leucine was slowly added and the resulting mixture was stirred until the amino acid was dissolved or well dispersed. Afterward, methocel was slowly added and the mixture was stirred until methocel was completely dissolved. The solution could be warmed up to dissolve methocel, if necessary. The resulting excipient solution was allowed to cool to room temperature and pass through 80 mesh screen. Then, 127.9g of screened excipient solution was added to a glass container and placed in an ice bath for 0.5 to 1 hour until the solution reached 0 °C. Next, SP-304 was added into the cold excipient solution. The mixture was stir vigorously to allow the peptide to dissolve in the cold solution. The resulting peptide solution was kept cold in the ice bath as a spraying/coating solution.

Drug Layering

[193] A Glatt GPCG-2 fluid bed processor (with top spray tower) with a Wurster insert was set up for drug layering onto Avicel PH 102 beads. After loading the Wurster column with Avicel

PH 102 beads, temperature was raised to 35 °C and maintained for 30 minutes with minimum fluidization of the beads. The bed temperature was reduced until an exhaust temperature of 35 °C was achieved. The pump tubing of the peristaltic pump used was primed by circulating the spraying solution mentioned above. After the spraying apparatus was adjusted to obtain a satisfactory spray pattern, the coating solution was sprayed onto Avicel PH 102 beads until all coating solution was sprayed. Operating parameters were recorded. The bed temperature and fluidization were maintained until the beads were sufficiently dry. The fluidization was then reduced while the bed temperature was maintained at 35 °C for 10 minutes. 2g of beads were sampled for moisture analysis when the bed temperature was kept at 35 °C. When the moisture of the sampled beads reached < 5% moisture, the coated beads were discharged and loaded into a dry container. LOD (loss on drying) <5%.

[194] The net weight of the coated blend was determined for calculation of the amount of magnesium stearate needed to lubricate the blend. Then the magnesium stearate was added to the coated blend and the mixture was blended for 1 minute.

Compression

[195] A Fette tablet press was set up. Then the blend mixture was loaded into the powder hopper and tooling was installed. The weight of each tablet was set to be 90 mg±5% and hardness to be 4-6 Kp. The weight, hardness and thickness of tablets were measured and recorded every 5 to 10 minutes. Friability measurement was also performed to ensure satisfactory product.

Example 11: Composition of batch 1528-2850-RD (capsules) and process

Item No.	Ingredient	Concentration % w/w
1	SP-304	0.3246
2	Microcrystalline cellulose (Avicel PH 102)	99.43
3	Magnesium stearate	0.2500
4	HPMC capsule shells	n/a

	Total	100

[196] The dry blend process of making the batch 2850-RD is described below.

Blending:

[197] Avicel PH 102 was screened through a 60 mesh screen. V-blenders (1 Qt, 4Qt, and 16 Qt) were then dusted by the screened Avicel PH 102. SP-304 was screened through a 200 mesh screen and loaded into the 1-Qt V-blender. Then, about 80 g Avicel PH 102 was added into the 1-Qt blender and the mixture was blended for 10 minutes at 25 rpm. The mixture was then transferred to the 4-Qt V-blender which was pre-dusted by the screened Avicel PH 102. The 1-Qt blender was rinsed with Avicel and the rinse material was transferred to the 4-Qt blender. The rinsing was repeated until all SP-304 was transferred to the 4-Qt blender. About 200g Avicel was added to the 4-Qt V-blender and the mixture was blended for 10 minutes. The resulting blend was then screened through a 60 mesh screen and then transferred into the pre-dusted 16-Qt blender (dusted with 1500g Avicel). The 4-Qt blender was rinsed with Avicel and the rinse material was transferred to the 16-Qt blender. The remaining Avicel was added to the 16-Qt blender and the mixture was blended for 10 minutes. The resulting blend was passed through Comil and then returned to the 16-Qt blender and was further blended for 5 minutes. Proper amount of magnesium stearate was weighed, screened through a 60 mesh screen, and added into the 16-Qt blender. The resulting mixture was blended for 2 minutes.

Encapsulation

[198] A MG2 Planeta capsule filler was set up. Average weight of the empty capsule shells was determined and target capsule fill weight was calculated (±5%). The blend from the above process was added into the hopper of the capsule filler and encapsulation was started. Run weight parameters were manually adjusted. Resulting capsules were then sorted according to the target fill weight.

Example 12: Composition of batch 1528-2850B-RD (tablets) and process

Item No.	Ingredient	Concentration % w/w
1	SP-304	0.3246
2	Microcrystalline cellulose (Avicel PH 102)	99.43
3	Magnesium stearate	0.2500
	Total	100

[199] The dry blend process of making the batch 2850B-RD is described below.

Blending:

[200] Avicel PH 102 was screened through a 60 mesh screen. V-blenders (1 Qt, 4Qt, and 16 Qt) were then dusted by the screened Avicel PH 102. SP-304 was screened through a 200 mesh screen and loaded into the 1-Qt V-blender. Then, about 80 g Avicel PH 102 was added into the 1-Qt blender and the mixture was blended for 10 minutes at 25 rpm. The mixture was then transferred to the 4-Qt V-blender which was pre-dusted by the screened Avicel PH 102. The 1-Qt blender was rinsed with Avicel and the rinse material was transferred to the 4-Qt blender. The rinsing was repeated until all SP-304 was transferred to the 4-Qt blender. About 200g Avicel was added to 4-Qt V-blender and the mixture was blended for 10 minutes. The resulting blend was then screened through a 60 mesh screen and then transferred into the pre-dusted 16-Qt blender (dusted with 1500g Avicel). The 4-Qt blender was rinsed with Avicel and the rinse material was transferred to the 16-Qt blender. The remaining Avicel was added to the 16-Qt blender and the mixture was blended for 10 minutes. The resulting blend was passed through Comil and then returned to the 16-Qt blender and was further blended for 5 minutes. Proper amount of magnesium stearate was weighed, screened through a 60 mesh screen, and added into the 16-Qt blender. The resulting mixture was blended for 2 minutes.

Compression

[201] A Fette tablet press was set up. Then the blend mixture was loaded into the powder hopper and tooling was installed. The weight of each tablet was set to be 90 mg±5% and

hardness to be 4-6 Kp. The weight, hardness, and thickness of tablets were measured and recorded every 5 to 10 minutes. Friability measurement was also performed to ensure satisfactory product.

Example 13: Composition of dry blend tablet formulation 1528-3161-RD, 1mg for vacuum drying

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.176
2	Microcrystalline cellulose (Avicel PH 102)	98.57
3	Magnesium stearate	0.2500
	Total	100

Example 14: Composition of dry blend tablet formulation 1528-3162-RD, 1mg with low-moisture cellulose

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.176
2	Microcrystalline cellulose (Avicel PH 112)	97.09
3	Magnesium stearate	0.2500
	Total	100

Example 15: Composition of spray coated trehalose granules tablet formulation 1528-3170-RD, 1mg

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.176
2	Trehalose granules	70.48
3	Methocel ES Premium LV	0.50
4	Histidine (in coating solution)	0.9225
5	Calcium ascorbate	0.100
6	Purified water	N/A
7	Trehalose powder (in coating solution)	1.0176
8	Microcrystalline cellulose (Avicel PH 200)	25.00
9	Histidine	0.5535
10	Magnesium stearate	0.2500
	Total	100

The process for making spray coated trehalose Granules tablet formulation 1528-3170-RD is described below.

Preparation of the Coating Dispersion

[202] Add purified water to labeled container and begin stirring. Stir such that a liquid vortex is produced without introducing air into liquid. Slowly add Methocel to solution. Stir until methocel is completely dissolved. Warm the solution if necessary to dissolve Methocel (≤ 50 ºC). Solution must be cooled before adding other materials. Add Trehalose to solution. Stir until materials are dissolved. Add Calcium Ascorbate to solution. Stir until materials are dissolved. Adjust pH to 7.0 with 1N NaOH solution if pH >7.0. Record adjusted pH. Place the Coating Solution in an ice bath and allow it stay in the batch for 0.5 to 1 hour until it reaches the ice temperature. Check with a thermometer to ensure at ice temperature. Weigh portions of required amount of API on a weighing boat and add each portion carefully to the cold Excipient Solution. Stir vigorously to allow peptide wetting and dissolving in the cold solution. Total amount of peptide must equal 14.107 g. Continue stirring solution such that a liquid vortex is produced without introducing air into liquid. Stir until PLECANATIDE is completely dissolved. Keep peptide solution cold all the time in the ice bath. Add Histidine to solution. Stir not more than 10min to dissolve the material. Obtain final pH of the Coating Solution. Obtain net weight of the Coating Solution. Coating Solution must be used within 30min to avoid coloration.

Drug Layering

[203] Setup Glatt GPCG2 with Wurster insert according to SOP EQP-OCM-064 for drug layering onto Trehalose Granules with coating dispersion. Use Glatt GPCG2 In-process form, "EQP-OCM-064-F1," to record in-process information. Turn unit on and preheat column. Fluid Bed Processor: Glatt GPCG-2. Filter: 200 micron screen. Product Container: 4" wurster, stainless steel. Insert height from bottom: 1". Spray direction: Top Spray. Fluid Nozzle Size/ Type: 1mm. Pump: Peristaltic, Master Flex LS. Tubing: Nalge #14 Silicon. Bed Temperature: ≤ 40°C. Inlet air temperature: Adjust to meet bed temperature target. Outlet air temperature: Monitor & record. Spray rate: initial rate 4-6g/min, adjust as required. Atomizing air pressure: 20 psi. Air flow: 60cmh and adjust for fluidization. Prepare double polyethylene bags large enough to hold drug layered Granules. Load column with Trehalose. Increase bed temperature to 35°C and maintain for 30 minutes with minimum fluidization of the Granules. Reduce bed temperature until an exhaust temperature of 35 °C is achieved. Prime pump tubing by circulating spraying solution; must not use more than 40g for tubing priming. Adjust the spraying apparatus to obtain satisfactory spray pattern. Coating Solution Weight after priming

should > 317g. Record initial weight below before spraying onto trehalose. Start spraying the coating solution onto Trehalose Granules. Record operating parameters on fluid bed processing form. Stop spraying when 297.2 g of coating solution has been sprayed. Maintain bed temperature and continue fluidization until Granules are sufficiently dry. Reduce fluidization and maintain bed temperature at 35°C for 10 minutes. Do not cool down the Granules. Sample 2g for moisture analysis until moisture is below 1%. Discharge coated Granules into pre-prepared and labeled container (with tare weight) lined with double polyethylene bag. Calculate net weight of drug layered Granules. Setup Lyophilizer per SOP EQP-OCM-00002. Load drug layered granules into a Lyoguard tray (Save bags). Use recipe 3 to dry blend overnight. Discharge dried blend into saved polyethylene bags. Obtain final moisture of the dried granules. Record final Moisture (<1%). Calculate net weight of dried Granules.

Blending

[204] Screen required Avicel and pass through 60 mesh screen. Setup 4 qt V-blender per SOP EQP-OCM-00056. Weigh amount of Histidine needed and blend with small amount of Avicel weighed. Charge into 4 qt. V-blender. Transfer Plecanatide Dried Granules into the V-Blender. Rinse 2-3 times the Lyoguard tray from Step 24 with adequate amount of Weighed Avicel .Transfer rinses into 4 qt. V-b;ender. Transfer all remaining Pre-weighed/screened Avicel into the V-Blender. Mix for 15 minutes. Weigh and screen Magnesium Stearate through a 60 mesh screen. Charge Magnesium Stearate to the 4 qt V-Blender. Ensure the cover is securely closed with no potential powder leakage during blending. Blend for 2 minutes.

Compression

[205] Set-up Korsch press per SOP EQP-OCM-00087. Install 0.250" Standard Concave Round Plain tolling. Obtain blend Assay results and calculate Target Tablet Weight. Acceptable weight range of tablets is ± 5.0%. Load the Final Blend into the powder hopper. Refill as necessary. Adjust fill weight to obtain tablets in the range of 95.0 - 105.0mg and hardness in the range of 4-6kP. Verify friability is NMT 1.0%. Check 5 tablet weights periodically every 5-10min to ensure tablet weight is within the range and record on form QRA-DOC-00011-F6. After tablet weights are recorded, obtain and record 3 tablet hardness and thickness during the periodic

weight check. Continue to compress acceptable tablets until the blend is used up. Once press is running properly to achieve specifications above, perform final Friability test and record results (Spec: NMT 1.0%).

Example 16: Composition of spray coated trehalose granules tablet formulation 1528-3171-RD, 1mg

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.167
2	Trehalose granules	70.31
3	Methocel ES Premium LV	0.50
4	Arginine	1.657
5	Calcium ascorbate	0.100
6	Water for injection	N/A
7	Trehalose powder (in coating solution)	1.0176
8	Microcrystalline cellulose (Avicel PH 200)	25.00
9	Magnesium stearate	0.2500
	Total	100

[206] The process for making spray coated trehalose Granules tablet formulation 1528-3171-RD is described below.

Preparation of Coating Solution

Add purified water (Item 6) to labeled container and begin stirring. Stir such that a liquid vortex is produced without introducing air into liquid. Slowly add Methocel to solution. Stir until methocel is completely dissolved. Warm the solution if necessary to dissolve Methocel (≤ 50 ºC). Record appearance of solution. Solution must be cooled before adding other materials. Add Trehalose to solution. Stir until materials are dissolved. Record appearance of solution. Add Arginine to solution. Stir until materials are dissolved. Record appearance of solution. Add Calcium Ascorbate to solution. Stir until materials are dissolved. Record appearance of solution. Adjust solution pH to pH 8.5 - 8.6 with concentrated HCl followed by adjust pH to 8.3 – 8.4 with 10N HCl. Record final adjusted pH. Place the Coating Solution in an ice bath and allow it stay in the batch for 0.5 to 1 hour until it reaches the ice temperature. Check with a thermometer to ensure at ice temperature. Weigh portions of required amount of API on a weighing boat and add each portion carefully to the cold Excipient Solution. Stir vigorously to allow peptide wetting and dissolving in the cold solution. Total amount of peptide must equal 14.006 g. Continue stirring solution such that a liquid vortex is produced without introducing air into liquid. Stir until PLECANATIDE is completely dissolved. Keep peptide solution cold all the time in the ice bath. Weigh 5.0g of WFI to rinse API container. Carefully rinse the side of coating solution container and completely transfer the rinse back to the coating solution container. Obtain final pH of the Coating Solution. Obtain net weight of the Coating Solution (~360.3 g). Coating Solution must be used within as soon as possible.

Drug Layering

[207] Setup Glatt GPCG2 with Wurster insert according to SOP EQP-OCM-064 for drug layering onto Trehalose Granules with coating dispersion. Use Glatt GPCG2 In-process form, "EQP-OCM-064-F1," to record in-process information. Turn unit on and preheat column.

Fluid Bed Processor: Glatt GPCG-2. Filter: 200 micron screen. Product Container: 4" wurster, stainless steel. Insert height from bottom: 1". Spray direction: Top Spray. Fluid Nozzle Size/ Type: 1mm. Pump: Peristaltic, Master Flex LS. Tubing: Nalge #14 Silicon. Bed Temperature: ≤ 40°C. Inlet air temperature: Adjust to meet bed temperature target. Outlet air temperature: Monitor & record. Spray rate: initial rate 4-6g/min, adjust as required. Atomizing air pressure: 20psi. Air flow: 60cmh and adjust for fluidization. Load column with Trehalose G. Increase bed temperature to 35°C and maintain for 30 minutes with minimum fluidization of the

Granules. Reduce bed temperature until an exhaust temperature of 35 °C is achieved. Prime pump tubing with coating solution. Must not use more than 40g for tubing priming. Adjust the spraying apparatus to obtain satisfactory spray pattern. Record initial weight below before spraying onto trehalose. Start spraying the coating solution onto Trehalose Granules. Record operating parameters on fluid bed processing form. Stop spraying when 300.3 g of coating solution has been sprayed. Maintain bed temperature and continue fluidization until Granules are sufficiently dry. Reduce fluidization and maintain bed temperature at 35°C for 10 minutes. Do not cool down the Granules. Sample 2g for moisture analysis until moisture is below 1%. Discharge coated Granules into pre-prepared and labeled container (with tare weight) lined with double polyethylene bag. Calculate net weight of drug layered Granules. If moisture is > 1%, vacuum dry blend as follows: Setup Lyophilizer per SOP EQP-OCM-00002. Load drug layered granules into a Lyoguard tray. Use recipe 3 to dry blend overnight. Discharge dried blend into saved polyethylene bags. Obtain final moisture of the dried granules. Calculate net weight of dried Granules.

Blending

[208] Screen required Avicel and pass through 60 mesh screen. Setup 4 qt V-blender. Transfer Plecanatide Dried Granules into the V-Blender. Save bag for discharging final blend. Rinse 2-3 times the Lyoguard tray and bag with adequate amount of Weighed Avicel. Transfer rinses into 4 qt. V-b;ender. Transfer all remaining Pre-weighed/screened Avicel into the V-Blender. Mix for 20 minutes. Weigh and screen Magnesium Stearate through a 60 mesh screen. Charge Magnesium Stearate to the 4 qt V-Blender. Ensure the cover is securely closed with no potential powder leakage during blending. Blend for 2 minutes. Sample 3 x 350 mg of blend at three locations. Obtain exact weight of each sample that has been transferred into the sampling bottle.

Compression

Set-up Korsch press per SOP EQP-OCM-00087. Install 0.250" Standard Concave Round Plain tolling. Obtain blend Assay results and calculate Target Tablet Weight. Acceptable weight range of tablets is ± 5.0%. Load the Final Blend into the powder hopper. Refill as necessary. Adjust fill weight to obtain tablets in the range of 95.0 - 105.0mg and hardness in the range of 4-6kP.

Verify friability is NMT 1.0%. Check 5 tablet weights periodically every 5-10min to ensure tablet weight is within the range. After tablet weights are recorded, obtain and record 3 tablet hardness and thickness during the periodic weight check. Continue to compress acceptable tablets until the blend is used up. Once press is running properly to achieve specifications above, perform final Friability test and record results (Spec: NMT 1.0%).

Example 17: Composition of spray coated trehalose granules tablet formulation 1528-3172, 1mg

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.167
2	Trehalose granules	70.81
3	Methocel ES Premium LV	0.50
4	TRIS	1.1524
5	Calcium ascorbate	0.100
6	Water for injection	N/A
7	Trehalose powder (in coating solution)	1.0176
8	Microcrystalline cellulose (Avicel PH 200)	25.00
9	Magnesium stearate	0.2500
	Total	100

[209] The process for making spray coated trehalose granules tablet formulation 1528-3172-RD is described below.

Preparation of Coating Solution

[210] Add purified water to labeled container and begin stirring. Stir such that a liquid vortex is produced without introducing air into liquid. Slowly add Methocel to solution. Stir until methocel is completely dissolved. Warm the solution if necessary to dissolve Methocel (≤ 50°C). Record appearance of solution.

[211] Solution must be cooled before adding other materials. Add Trehalose to solution. Stir until materials are dissolved. Record appearance of solution. Add TRIS to solution. Stir until materials are dissolved. Record appearance of solution. Add Calcium Ascorbate to solution. Stir until materials are dissolved. Record appearance of solution. Obtain solution pH: Adjust pH to pH 7.8 – 7.9 with concentrated HCl followed by adjust pH to 7.7 – 7.6 with 10N HCl. Record final adjusted pH. Place the Coating Solution in an ice bath and allow it stay in the batch for 0.5 to 1 hour until it reaches the ice temperature. Check with a thermometer to ensure at ice temperature. Weigh portions of required amount of API on a weighing boat and add each portion carefully to the cold Excipient Solution. Stir vigorously to allow peptide wetting and dissolving in the cold solution. Total amount of peptide must equal 14.006 g. Continue stirring solution such that a liquid vortex is produced without introducing air into liquid. Stir until PLECANATIDE is completely dissolved. Keep peptide solution cold all the time in the ice bath. Weigh 5.0g of WFI to rinse API container. Carefully rinse the side of coating solution container and completely transfer the rinse back to the coating solution container. Obtain final pH of the Coating Solution. Obtain net weight of the Coating Solution (~354.2 g). Coating Solution must be used as soon as possible.

The blending and compression processes for batch 1528-3172-RD are similar to that described above for batch 1528-3171-RD.

Example 18: Composition of 1mg dry blend tablet formulation 1528-2925-RD

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.106
2	Microcrystalline cellulose (Avicel PH	98.64

	102)	
3	Magnesium stearate	0.2500
	Total	100

Example 19: Composition of 3mg dry blend tablet formulation 1528-2926-RD

Item No.	Ingredient	Concentration % w/w
1	SP-304	3.318
2	Microcrystalline cellulose (Avicel PH 102)	96.43
3	Magnesium stearate	0.2500
	Total	100

[212] Other batches were prepared by the processes similar to those described in Examples 9-12. Their compositions are listed below.

[213] Batch 500-55: 0.33% plecanatide, 95.17% microcyrstalline cellulose, 4.0% sodium starch glycolate, and 0.5% magnesium stearate.

[214] Batches 1528-2907-RD and 2010F100A: 3.318% plecanatide, 96.43% Avicel, and 0.25% Mg stearate.

[215] Batches 1528-2906-RD and 2010F099A: 1.106% plecanatide, 98.65% Avicel, and 0.25% Mg stearate.

[216] Batches 1528-2890-RD and 2010F101A: 0.3246% plecanatide, 99.43% Avicel, and 0.25% Mg stearate.

[217] Formula compositions for batches 11H141, 11H152, and 11H140 in this table below (not previously disclosed) are the same as the formula compositions for GMP stability batches 2010F101A, 2010F099A, and 2010F100A, respectively.

Example 20: Plecanatide tablet and capsule stability

[218] Capsules and tablets of different batches were tested for their stability and the results were provided. Unless otherwise specified, 1M, 2M, 3M, or 4M in the tables below denotes that the measurements were carried out at the end of 1, 2, 3, or 4 month(s) of the storage period.

Potency Summary: This test was performed by taking a composite sample of about 5 units to determine the average potency of the sample. The table below shows the stability of capsules or tablets in terms of potency (% of label claim).

Lot (description)	Potency (% Label Claim)																		
	Bulk*	Package	Storage Condition																
		Package	Initial	40C/75RH			30C/65RH			25C/60RH					5C				
				1M	2M	3M	1M	2M	3M	1M	2M	3M	7M	10M	1M	2M	3M	4M	7M	8.5M
1528-2850-RD (0.3mg dry blend capsules)	88	HDPE bottle		89		87			89			91		80				89.3		89
		Oxyguard bottle		91		91			92			91		79				88.9		90
		Blister strip	90	90		85			88			91		79						90
1528-2855-RD (0.3mg coated bead capsule)	94	HDPE bottle		101		100			96			102		88						98
		Oxyguard bottle		101		96			99			104		87						100
		Blister strip		97		103			99			98		87						97
500-55 (0.3mg dry blend capsule)	97	HDPE bottle		97		94			95			96		84						98
		Oxyguard bottle		98		96			96			102		83						97
		Blister strip	93	97		93			95			106		83						96
1528-2850B-RD (0.3mg dry blend tablet)	76	HDPE bottle		85		88			94			83		67						70
		Oxyguard bottle		84		84			88			74		74						80
1528-2851-RD (0.3mg coated particle tablet)	96	HDPE bottle		115		72			90			99		99						78
		Oxyguard bottle		81		88			83			111		85						96
2010F100A (3mg dry blend capsule)	101	Blister strip	97	95	94	91	95	95	92	97	95	93			97	94	94			
2010F101A (0.3mg dry blend capsule)	97	Blister strip	92	91	91	86	94	92	85	95	93	88			95	95	92			
2010F099A (1mg dry blend capsule)	98	Blister srtip	94	92	91	89	93	94	89	94	94	91			95	94	92			
11H141 (0.3mg dry blend	103	Blister strip	101	95	92	87	98	93	92	96	92	95			100	97	97			

capsule)																				
11H152 (1mg dry blend capsule)	102	Blister strip	97	91	91	93	94	95	96	96	95	96			97	95	97			
11H140 (3mg dry blend capsule)	105	Blister strip	99	94	95	94	95	94	97	99	95	97			99	97	97			
1528-2925-RD (1mg dry blend tablet)	99	Oxyguard 40cc with PharmaKeep											99						103	
1528-2926-RD (3mg dry blend tablet)	100	Oxyguard 40cc with PharmaKeep											94						93	
1528-2907-RD (3mg dry blend capsule)	98																			
1528-2906-RD (1mg dry blend capsule)	98																			
1528-2890-RD (0.3mg dry blend capsule)	93																			

*Blend

[219] As demonstrated by the table above, there was little or no appreciable loss in potency after storage under accelerated conditions (40C/75RH or 30C/65RH), which suggests that these capsules or tablets could be stable at room temperature for 18 months or for longer times if refrigerated or stored at 25C.

[220] Water content summary: The table below shows that the water content was stable over the testing period in the packages evaluated for various capsule/tablet compositions. This further demonstrated that products were stable.

[221]

Lot	Water	Packaging	Water packaged product

	(in-process)		Initial	40C/75RH			30C/65RH			25C/60RH					5C					
				1M	2M	3M	1M	2M	3M	1M	2M	3M	7M	10M	1M	2M	3M	4M	7M	8.5M
1528-2850-RD 0.3mg dry blend capsule		32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		5.03		5.64			3.00			2.22		2.39				5.48		1.8
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		5.07		5.24			4.28			5.33		4.08				5.31		3.7
		Blister, N2	4.21	4.87		5.80			4.76			4.31		4.09						2.8
1528-2855-RD 0.3mg coated bead capsule	2.40	32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		0.57		0.47			1.63			0.68		0.42						0.2
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		2.10		1.05			1.29			2.07		0.30						0.8
		Blister strip		0.73		2.11			0.54			0.58		0.32						0.3
500-55 0.3mg dry blend capsule		HDPE bottle		5.63		4.19			5.51			5.79		2.98						2.7
		Oxyguard bottle		5.78		4.69			5.90			5.66		2.99						2.8
		Blister strip	4.09	5.78		4.17			5.53			6.16		3.12						2.9
1528-2850B-RD 0.3mg dry blend tablet		32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		4.09		4.03			6.28			6.10		2.86						2.1
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		4.81		4.91			6.15			6.30		4.05						3.4
1528-2851-RD 0.3mg coated particle tablet	3.32	32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		4.33		4.50			5.09			5.90		2.55						1.5
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		5.15		4.88			5.82			6.02		4.34						3.0
2010F100A (3mg dry blend capsule)		Blister strip	4.7	4.5	4.6	4.4	4.5	4.7	4.4	4.5	4.8	4.4			4.5	4.8	4.5			
2010F101A (0.3mg dry blend capsule)		Blister strip	4.5	4.8	4.7	4.7	4.5	4.7	4.3	4.4	4.7	4.3			4.5	4.7	4.2			
2010F099A (1mg dry blend capsule)		Blister strip	4.6	4.4	4.6	4.4	4.5	4.5	4.3	4.4	4.6	4.4			4.2	4.7	4.3			

11H141 (0.3mg dry blend capsule)		Blister strip	5	4.8	4.9	4.9	5.1	4.9	4.8	5.0	5.0	4.9			5.0	4.9	4.9			
11H152 (1mg dry blend capsule)		Blister strip	5.2	4.8	4.9	4.8	4.8	4.8	4.9	4.8	4.8	4.9			5.0	4.9	4.8			
11H140 (3mg dry blend capsule)		Blister strip	5.2	5.0	5.0	5.0	4.9	5.0	5.0	4.9	5.0	4.9			4.9	4.9	4.8			
1528-2925-RD (1mg dry blend tablet)		Oxyguard 40cc with PharnaKeep											4.9						4.0	
1528-2926-RD (3mg dry blend capsule)		Oxyguard 40cc with PharnaKeep											4.0						4.0	
1528-2907-RD 3mg dry blend capsule		Bulk capsule	4.78																	
1528-2906-RD 1m dry blend capsule		Bulk capsule	4.84																	
1528-2890-RD		Bulk capsule	4.8																	

[222]

Impurity summary: The table below shows the product stability in terms of HPLC or UPLC of total impurities as a function of time and storage condition. The data in the table suggest that the increase in total impurities in tested batches except batch 500-55 be no greater than 7% at room temperature after 18 months. It also suggest that the increase in total impurities in all tested 1528-2855-RD batche in different packages be no greater than 7% at 30 °C for 18 months. It was also observed that the 1528-2855-RD batch had less impurity increase than the 1528- 2850-RD batch or was more stable than the 1528-2850-RD batch.

Batch	Package	Total impurities % area																	
		Initial	40C/75RH			30C/65RH			25C/60RH					5C					
			1M	2M	3M	1M	2M	3M	1M	2M	3M	7M	10M	1M	2M	3M	4M	7M	8.5M
1528-2850-RD	HDPE bottle	3.2	5.1		5.9			4.4			3.8		4.8				3.1		3.7
	Oxyguard bottle		5.7		7.4			5.3			4.3		5.3				3.1		3.5
	Blister strip		5.5		7.0			5.0			4.3		5.5						3.7
1528-2855-RD	HDPE bottle	3.5	3.6		5.1			3.8			3.4		4.4						3.4
	Oxyguard bottle		3.9		4.4			4.1			3.7		4.0						3.7
	Blister strip		4.0		5.2			4.0			3.6		4.2						3.8
500-55	HDPE bottle	3.2	5.7		8.4			5.4			4.4		6.0						3.5
	Oxyguard bottle		5.6		7.0			5.1			4.3		5.6						3.5
	Blister strip		6.5		8.0			5.7			4.8		6.5						3.6
1528-2850B-RD	HDPE bottle	3.6	5.0		6.5			4.5			3.9		4.7						3.7
	Oxyguard bottle		5.6		7.3			4.7			4.1		4.9						3.6
1528-2851-RD	HDPE bottle	3.7	4.2		5.1			4.0			3.8		3.9						3.7
	Oxyguard bottle		4.9		6.8			4.7			4.4		4.3						3.9
2010F101A (0.3mg dry blend capsule)	Blister strip	2.1	4.4	3.9	4.7	2.9	3.2	3.4	3.1	2.7	3.2			2.0	1.3	2.0			
2010F099A (1mg dry blend capsule)	Blister strip	2.9	3.7	3.8	4.3	3.1	3.1	3.6	2.7	2.9	3.2			2.4	2.4	2.4			
2010F100A (3mg dry blend capsule)	Blister strip	2.4	3.2	3.6	4.2	2.8	2.8	3.0	2.6	2.7	2.9			2.4	2.5	2.7			

11H141 (0.3mg dry blend capsule)	Blister strip	1.3	3.3	4.2	4.5	2.5	3.6	3.3	2.0	2.8	2.9			1.4	1.5	1.8			
11H152 (1mg dry blend capsule)	Blister strip	2.4	3.6	4.2	4.1	2.6	3.2	3.1	2.6	3.1	2.9			2.3	2.3	2.1			
11H140 (3mg dry blend capsule)	Blister strip	2.1	3.5	3.7	4.5	2.6	2.7	3.3	2.5	2.7	2.9			2.3	2.2	1.8			
1528-2925-RD (1mg dry blend tablet)	Oxyguard 40cc with PharnaKeep											2.7						1.7	
1528-2926-RD (3mg dry blend capsule)	Oxyguard 40cc with PharnaKeep											2.6							
1528-2906-RD	HDPE bottle	1.83		5.18															
1528-2907-RD	HDPE bottle	1.85		4.58															
1528-2890-RD	Bulk	1.9																	

Content uniformity: This test was performed by placing 10 individual capsule/tablet units in 10 individual bottles and potency of each unit was measured to show whether individual capsules or tablets have uniform potency (% label claim or %LC).

0.3mg Dry blend tablet 1528-2850B-RD	
	%LC
Sample	**1528-2850B-RD (dry tabs)**
1	78.62
2	91.43
3	86.52
4	90.9
5	84.83
6	95.29
7	75.69
8	76.87
9	84.92
10	86.9
Mean	**85.2**
std. dev	6.51
% RSD	**7.64**

0.3mg Coated particle tablet 1528-2851-RD		
Sample	**Weight (mg)**	**% Label Claim**
1	88.86	69.55
2	89	94.41
3	88.89	94.34
4	88.6	72.18
5	88.37	142.52
6	88.76	149.44

7	89.42	78.8
8	88.56	131.08
9	89.08	102.55
10	88.78	99.13
Mean		103.4
St. Dev		28.53
%RSD		27.59

0.3mg Dry blend capsule 1528-2890			3mg Dry blend capsule 1528-2907-RD			1mg Dry blend capsule 1528-2906-RD	
Sample	%LC		Sample	%LC		Sample	%LC
1	87.2		1	94.5		1	98.1
2	94.6		2	101.2		2	101.8
3	92.6		3	97.9		3	93.1
4	94.2		4	94.5		4	97.5
5	93.5		5	95.9		5	97.9
6	91.7		6	95.2		6	97.1
7	91.6		7	96.1		7	94.5
8	99		8	99		8	100.1
9	91.8		9	93.8		9	98.1
10	92.1		10	93.4		10	97.9
Mean	92.8		Mean	96.2		Mean	97.6
RSD	3.20%		RSD	2.60%		RSD	2.50%
AV(10)***	12.8		AV(10)	8.4		AV(10)	6.8

***AV = acceptance value used for UPS <905> content uniformity. Idealy AV should be less than 15 to pass USP <905> content uniformity.

0.3mg dry blend capsule 1528-2850-RD		
Sample	Original %LC	Re -preparation %LC
1	82.73	85.87
2	84.57	89.45
3	80.29	91.39
4	84.88	88.45
5	85.2	86.96
6	82.9	84.84
7	84.75	86.21
8	86.58	91.37
9	84.34	88.79
10	88.82	84.75
Mean	84.51	87.81
std. dev	2.288445	2.467121
% RSD	2.7	2.8

Conte1528-2855-RD Sample	**%LC**		**1528-2850B-RD Sample**	**%LC**
1	88.82		1	78.62
2	93.73		2	91.43
3	89.06		3	86.52
4	84.94		4	90.9
5	89.93		5	84.83
6	88.7		6	95.29
7	88.71		7	75.69
8	86.85		8	76.87
9	86.92		9	84.92
10	91.33		10	86.9
Mean	**88.9**		**Mean**	**85.2**
std. dev	2.45		std. dev	6.51
% RSD	**2.76**		**% RSD**	**7.64**

500-55	
Sample	% label claim
1	96.90%
2	99.40%
3	103.20%
4	96.90%
5	100.00%
6	99.60%
7	96.90%
8	102.80%
9	96.80%
10	93.90%
Mean	98.60%
SD	2.91
RSD	3.00%
AV	7.1 (PASS)

[223] The data in the tables above show that all of the batches yield very good content uniformity acceptable for commercial product.

[224] Dissolution 50-rpm summary: The tables below are summaries of the dissolution of drug from capsules or tablets in an unconventional small-volume apparatus needed to measure the small amount of drug in the units using slow stirring to look for changes in dissolution over time. The test was performed by placing one unit into a very small volume of water at 37C with a paddle stirring at 50-rpm (which is slow) and data were collected at 15, 30 45, and 60 minutes to show the drug release rate over time. These tested products are "immediate release" oral solid dosage forms and a conventional requirement is to have about 75% released in about 45 minutes. The tables summarize the results at 45 minutes and indicate that dissolution was stable over time.

		Dissolution (% label claim at 45 minutes)						
		Initial		40C/75RH	30C/65RH		25C	5C
Lot (description)		bulk	0M	1M	2M	3M	3M	4M
1528-2850-RD (dry blend V-Cap capsule HDPE bottle)	Vessel 1	85		78	84	81	86	83
	Vessel 2	87		73	90	82	84	85
	Vessel 3	88		79	85	79	91	87
	Vessel 4	84		86	87	78	83	85
	Vessel 5	89		72	89	80	79	90
	Vessel 6	88		81	85	82	88	83
	Average	87		78	87	80	85	85
	RSD	2		6.4	2.7	2.1	5.0	2.9
1528-2850-RD (dry blend Vcap capsule OxyGuard bottle)	Vessel 1	85		69	89	79	88	82
	Vessel 2	87		75	89	87	81	85
	Vessel 3	88		77	87	86	84	86
	Vessel 4	84		80	87	83	83	80
	Vessel 5	89		71	88	89	84	84
	Vessel 6	88		76	88	79	86	89
	Average	87		75	88	84	84	84
	RSD	2		5.3	1.2	5.2	3.1	3.6
1528-2850-RD (dry blend V-cap capsule blister strip)	Vessel 1	85	75	59	86	73	83	
	Vessel 2	87	89	77	79	81	81	
	Vessel 3	88	88	83	87	74	84	
	Vessel 4	84	89	67	93	85	83	
	Vessel 5	89	93	75	82	82	84	
	Vessel 6	88	90	82	90	67	87	
	Average	87	87	74	86	77	84	
	RSD	2	7	12.5	6.3	8.6	2.4	

		Dissolution (% label claim at 45 minutes)				
		Initial	40C/75RH	30C/65RH		25C
Lot (description)		bulk	1M	2M	3M	3M
1528-2855-RD (coated bead V-Cap capsule HDPE bottle)	Vessel 1	104	85	100	79	83
	Vessel 2	89	90	97	83	88
	Vessel 3	91	84	71	91	50

	Vessel 4	88	64	73	94	88
	Vessel 5	94	75	72	75	92
	Vessel 6	93	80	39	96	94
	Average	93	**80**	**75**	**86**	**83**
	RSD	6	**12**	**29**	9.7	20
1528-2855RD (coated bead V-cap capsule OxyGuard bottle)	Vessel 1	104	88	80	87	78
	Vessel 2	89	79	91	86	94
	Vessel 3	91	84	63	92	74
	Vessel 4	88	92	98	90	98
	Vessel 5	94	89	81	81	93
	Vessel 6	93	44	99	81	78
	Average	93	**79**	**85**	**86**	**86**
	RSD	6	**23**	**16**	5.3	12.1
1528-2855-RD (coated bead V-cap capsule blister strip)	Vessel 1	104	85	98	100	81
	Vessel 2	89	84	94	63	80
	Vessel 3	91	97	96	82	87
	Vessel 4	88	94	96	55	74
	Vessel 5	94	64	75	95	66
	Vessel 6	93	96	102	89	82
	Average	93	**87**	**93**	**81**	**78**
	RSD	6	**14**	**10**	22.4	9.2

	Dissolution (% label claim at 45 minutes)				
		Initial	40C/75RH	30C/65RH	
Lot (description)		bulk	1M	2M	3M
1528-2851-	Vessel 1	58%	67	68	89

RD (coated particle tablet HDPE bottle)	Vessel 2	77%	84	78	124
	Vessel 3	57%	62	68	70
	Vessel 4	96%	110	84	105
	Vessel 5	95%	65	107	61
	Vessel 6	64%	103	76	51
	Average	74%	**82**	**80**	**83**
	RSD	24%	**26**	**18**	33
1528-2851-RD (coated particle tablet OxyGuard bottle)	Vessel 1	58%	89	54	118
	Vessel 2	77%	73	101	69
	Vessel 3	57%	75	82	80
	Vessel 4	96%	68	67	73
	Vessel 5	95%	76	162	96
	Vessel 6	64%	97	82	95
	Average	74%	**80**	**91**	**89**
	RSD	24%	**14**	42	**21**

	Dissolution (% label claim at 45 minutes)				
		Initial	40C/75RH	30C/65RH	
Lot (description)		bulk	1M	2M	3M
1528-2850B-RD (dry blend tablet HDPE bottle)	Vessel 1	90%	88	96	92
	Vessel 2	69%	79	82	92
	Vessel 3	83%	76	100	85
	Vessel 4	94%	96	86	94
	Vessel 5	88%	89	89	83
	Vessel 6	92%	83	97	83
	Average	86%	**85**	**92**	**88**
	RSD	11%	**8.2**	**8**	**5.6**
1528-2850B-RD (dry blend tablet OxyGuard bottle)	Vessel 1	90%	74	80	91
	Vessel 2	69%	97	87	95
	Vessel 3	83%	91	86	90
	Vessel 4	94%	94	91	90
	Vessel 5	88%	83	91	89
	Vessel 6	92%	91	76	84
	Average	86%	**88**	**85**	**90**
	RSD	11%	**9.6**	7	**4.0**

	Dissolution (% label claim at 45 minutes)						
		Initial		40C/75RH	30C/65RH		25C
Lot (description)		bulk	0M	1M	2M	3M	3M
500-55 (dry blend V-Cap Plus capsule HDPE bottle)	Vessel 1	95		90	92	91	89
	Vessel 2	98		85	98	97	98
	Vessel 3	69		85	96	94	76
	Vessel 4	94		89	95	100	97
	Vessel 5	99		89	97	98	86
	Vessel 6	104		100	99	94	92
	Average	93		**89**	**96**	**96**	**90**
	RSD	13.1		**6.2**	**2.4**	**3.6**	**9.1**
500-55 (dry blend V-Cap Plus capsule OxyGuard bottle)	Vessel 1	95		84	103	99	94
	Vessel 2	98		97	101	95	103
	Vessel 3	69		97	99	98	97
	Vessel 4	94		92	97	92	96
	Vessel 5	99		91	100	95	101
	Vessel 6	104		96	95	93	91
	Average	93		**93**	**99**	**95**	**97**
	RSD	13.1		**5.3**	**2.7**	**2.7**	**4.3**
500-55 (dry blend V-Cap Plus capsule foil blister)	Vessel 1	95	98	99		89	98
	Vessel 2	98	101	88		94	87
	Vessel 3	69	107	90		89	96
	Vessel 4	94	96	90		86	87
	Vessel 5	99	99	68		89	94
	Vessel 6	104	99	90		82	89
	Average	93	**100**	**87**		**88**	**92**
	RSD	13.1	**3.8**	**11.8**		**4.3**	**5.5**

Dry blend 3mg lot 1528-2907-RD 500-mL				
	15 min	30 min	45 min	60 min
Vessel 1	91	96	97	96
Vessel 2	96	95	97	96
Vessel 3	96	97	97	97
Vessel 4	95	102	100	100
Vessel 5	97	96	96	97
Vessel 6	92	99	98	98

Average	94	97	98	97
RSD	2.7	2.5	1.1	1.4

Dry blend 1mg lot 1528-2906-RD 150-mL				
	15 min	30 min	45 min	60 min
Vessel 1	65	92	96	99
Vessel 2	49	91	95	96
Vessel 3	46	88	96	97
Vessel 4	44	96	101	102
Vessel 5	39	78	93	99
Vessel 6	57	90	95	96
Average	50	89	96	98
RSD	18.8	7	2.8	2.4

Dry blend 0.3mg lot 1528-2890-RD 50-mL				
	15 min	30 min	45 min	60 min
Vessel 1	57	94	100	105
Vessel 2	60	96	100	105
Vessel 3	86	93	94	95
Vessel 4	76	90	91	101
Vessel 5	69	90	97	106
Vessel 6	68	95	97	97
Average	69	93	97	102
RSD	15.6	2.8	3.4	4.5

	Capsule Dissolution at 45 minutes												
		5C			**25C**			**30C**			**40C**		
Lot (strength)	COA	1M	2M	3M	1M	2M	3M	1M	2M	3M	1M	2M	3M
2011F101 A (0.3mg)	98%	99%	95%	95%	95%	92%	95%	94%	93%	97%	93%	90%	92%
2011F099 A (1mg)	96%	95%	95%	95%	91%	93%	94%	93%	90%	95%	95%	92%	93%
2011F100 A (3mg)	99%	101%	97%	97%	100 %	95%	95%	98%	95%	95%	96%	93%	95%
11H141 (0.3mg)	101%	102%	101 %	101 %	105 %	96%	106 %	102 %	97%	103 %	99%	96%	98%
11H152 (1mg)	96%	96%	99%	97%	96%	99%	97%	96%	96%	98%	96%	96%	98%
11H140 (3mg)	102%	102%	102 %	101 %	105 %	100%	97%	102 %	99%	102 %	101 %	99%	96%

[225] Dissolution 75-rpm: The tables below show a few examples where the stirring rate was increased slightly to 75-rpm to give more consistent results and indicates stable dissolution after accelerated storage of 1 or 2 months at 40C 75% relative humidity.

Dry blend 0.3mg lot 1528-2850-RD 1M 40C/75RH 75-rpm 50-mL				
	15 min	30 min	45 min	60 min
Vessel 1	75	80	80	81
Vessel 2	61	75	80	82
Vessel 3	65	81	83	84
Vessel 4	78	86	84	85
Vessel 5	66	79	83	84
Vessel 6	62	79	84	86
Average	68	80	82	84
RSD	10.3	4.5	2.3	2.2

Dry blend 1mg lot 1528-2906A-RD 2M 40C/75RH 75-rpm 50-mL				
	15 min	30 min	45 min	60 min
Vessel 1	69	84	88	88
Vessel 2	62	82	84	85
Vessel 3	65	82	85	85
Vessel 4	58	70	80	79
Vessel 5	59	77	82	81
Vessel 6	68	80	83	84
Average	64	79	84	84
RSD	7.2	6.4	3.3	3.8

[226] 2855-RD dissolution: The tables below are all the dissolution profiles of batch 1528-2850-RD and indicate stable drug release over time.

	Initial Percent Dissolved			
Vessel	**15**	**30**	**45**	**60**
1	84%	99%	104%	104%
2	28%	80%	89%	92%
3	68%	83%	91%	95%
4	56%	79%	88%	98%

5	29%	83%	94%	98%
6	74%	85%	93%	96%
Mean	57%	85%	93%	97%
RSD	41.20%	8.50%	6.00%	4.20%

1M 40C/75RH OxyGuard Packaging					2M 30C/65RH OxyGuard				3M 30C/65RH OxyGuard				3M 25C/60RH OxyGuard			
Vessel	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	35	74	88	93	47	67	80	90	76	83	87	88	44	62	78	85
2	46	74	79	85	57	80	91	95	65	79	86	91	70	89	94	97
3	39	78	84	88	43	55	63	71	64	84	92	97	48	62	74	79
4	59	82	92	94	753	92	98	101	71	85	90	94	65	92	98	103
5	22	82	89	92	38	64	81	92	60	75	81	87	72	86	93	96
6	4	20	44	61	54	94	99	101	55	74	81	87	53	74	78	84
Average	**34**	**68**	**79**	**86**	**52**	**75**	**85**	**92**	**65**	**80**	**86**	**91**	**59**	**78**	**86**	**91**
RSD	**57**	**35**	**23**	**14**	**25**	**21**	**16**	**12**	11.7	5.7	5.3	4.6	20.1	17.4	12.1	10.4

1M 40C/75RH HDPE Bottle					2M 30C/65RH HDPE				3M 30C/65RH HDPE				3M 25C/60RH HDPE			
Vessel	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	61	78	85	89	78	97	100	103	58	72	79	85	54	70	83	92
2	63	83	90	92	77	93	97	98	51	72	83	90	66	81	88	92
3	66	79	84	91	41	59	71	78	53	84	91	94	10	29	50	66
4	25	44	64	77	50	65	73	78	66	89	94	95	69	81	88	92
5	47	67	75	80	37	59	72	83	48	66	75	81	68	83	92	97
6	57	71	80	85	6	21	39	52	85	94	96	99	82	91	94	97
Average	**53**	**70**	**80**	**86**	**48**	**66**	**75**	**82**	**60**	**80**	**86**	**91**	**58**	**73**	**83**	**89**
RSD	**28**	**20**	**12**	7	**56**	**42**	**29**	**22**	22.6	14	9.7	7.3	43	30.6	19.6	13.3

1M 40C/75RH Blister Packaging					2M 30C/65RH Blister				3M 30C/65RH Blister				3M 25C/60RH Blister			
Vessel	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	36	69	85	90	61	91	98	100	82	95	100	102	53	71	81	90
2	41	69	84	88	57	82	94	100	31	48	63	74	27	57	80	87

3	67	96	97	98		63	87	96	100		69	77	82	85		70	78	87	92
4	54	83	94	104		36	80	96	100		29	41	55	69		52	66	74	87
5	10	46	64	79		45	61	75	83		84	94	95	97		25	48	66	80
6	70	91	96	100		87	100	102	104		74	84	89	82		50	74	82	84
Average	**47**	**76**	**87**	**93**		**58**	**83**	**93**	**98**		**62**	**73**	**81**	**85**		**46**	**66**	**78**	**87**
RSD	**48**	**25**	**14**	**10**		**30**	**16**	**10**	**8**		40.5	32.1	22.4	14.9		37.0	17.0	9.2	5.3

[227] Bathes 2850-RD, 2850B-RD, 2851-RD, and 500-55 were also tested in the similar fashion and all showed stable drug release over time.

We claim:

1. A method for treating chronic constipation in a human subject comprising orally administering to said human subject a composition consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months.

2. The method of claim 1, wherein the constipation is associated with irritable bowel syndrome or chronic idiopathic constipation.

3. A method of treating or alleviating a symptom associated with chronic idiopathic constipation or irritable bowel syndrome in a human subject comprising orally administering to said human subject a composition consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months.

4. The method of claim 3, wherein the symptom is constipation or abdominal pain.

5. The method of claim 1, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

6. The method of claim 5, wherein said inhibitor of cGMP-dependent phosphodiesterase is selected from the group consisting of sulindac sulfone, zaprinast, and motapizone.

7. The method of claim 1, further comprising administering to said patient an effective dose of a laxative.

8. The method of claim 3, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

9. The method of claim 8, wherein said inhibitor of cGMP-dependent phosphodiesterase is selected from the group consisting of sulindac sulfone, zaprinast, and motapizone.

10. The method of claim 3, further comprising administering to said patient an effective dose of a laxative.

11. The method of claim 1, wherein the inert low moisture carrier is microcrystalline cellulose.

12. The method of claim 1, wherein the lubricant is magnesium stearate.

13. The method of claim 1, wherein the inert low moisture carrier is microcrystalline cellulose and the lubricant is magnesium stearate.

14. The method of claim 3, wherein the inert low moisture carrier is microcrystalline cellulose.

15. The method of claim 3, wherein the lubricant is magnesium stearate.

16. The method of claim 3, wherein the inert low moisture carrier is microcrystalline cellulose and the lubricant is magnesium stearate.

ABSTRACT OF THE DISCLOSURE

The invention provides low-dose formulations of guanylate cyclase-C ("GCC") agonist peptides and methods for their use. The formulations of the invention can be administered either alone or in combination with one or more additional therapeutic agents, preferably an inhibitor of cGMP-dependent phosphodiesterase or a laxative.

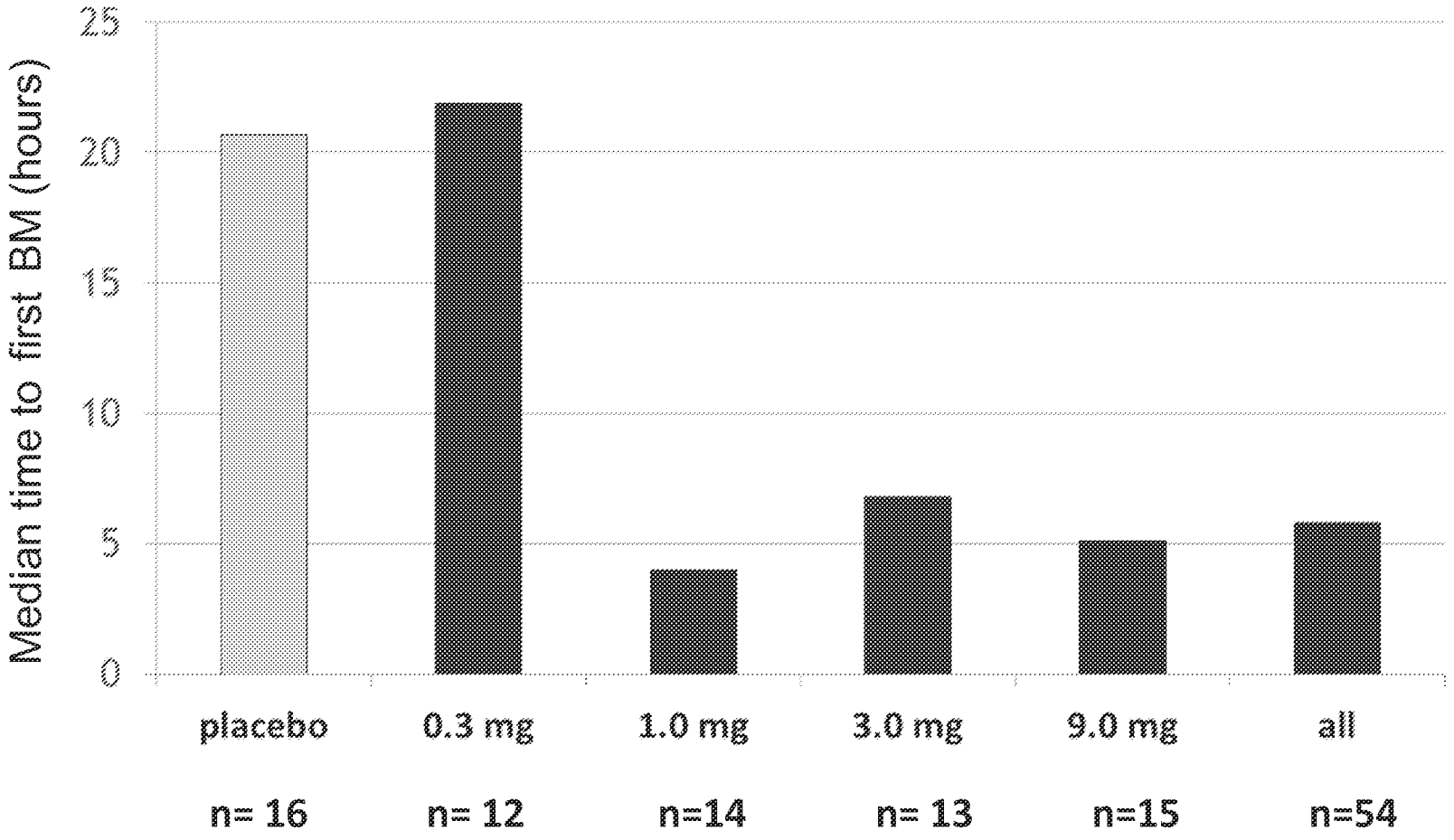
Median time to first BM (hours)
25
20
15
10
5
0
placebo
0.3 mg
1.0 mg
3.0 mg
9.0 mg
all
n= 16
n= 12
n=14
n= 13
n=15
n=54

Fig. 1

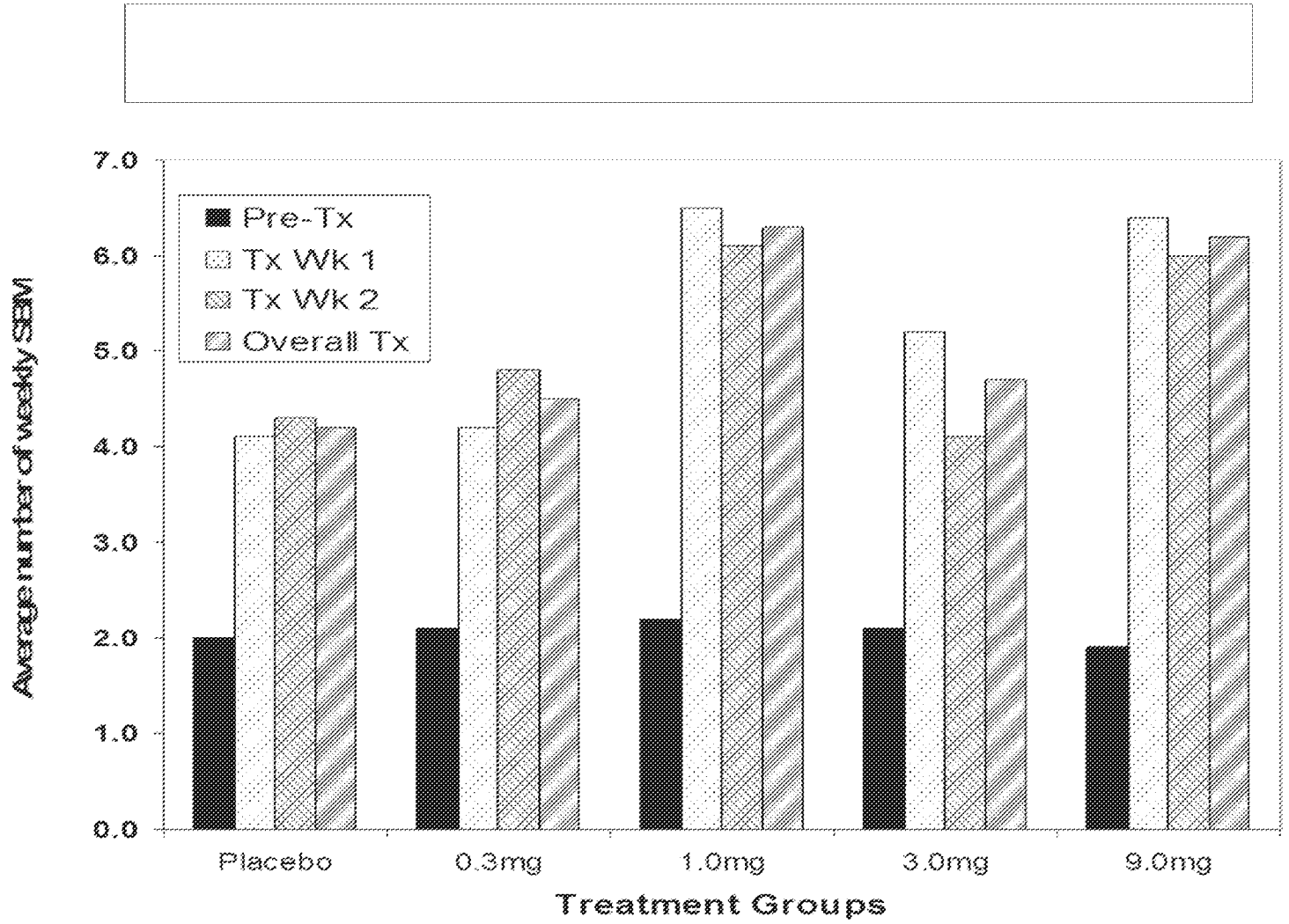
Pre-Tx
Tx Wk 1
Tx Wk 2
Overall Tx
Average number of weekly SEM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Placebo
0.3mg
1.0mg
3.0mg
9.0mg
Treatment Groups

Fig. 2

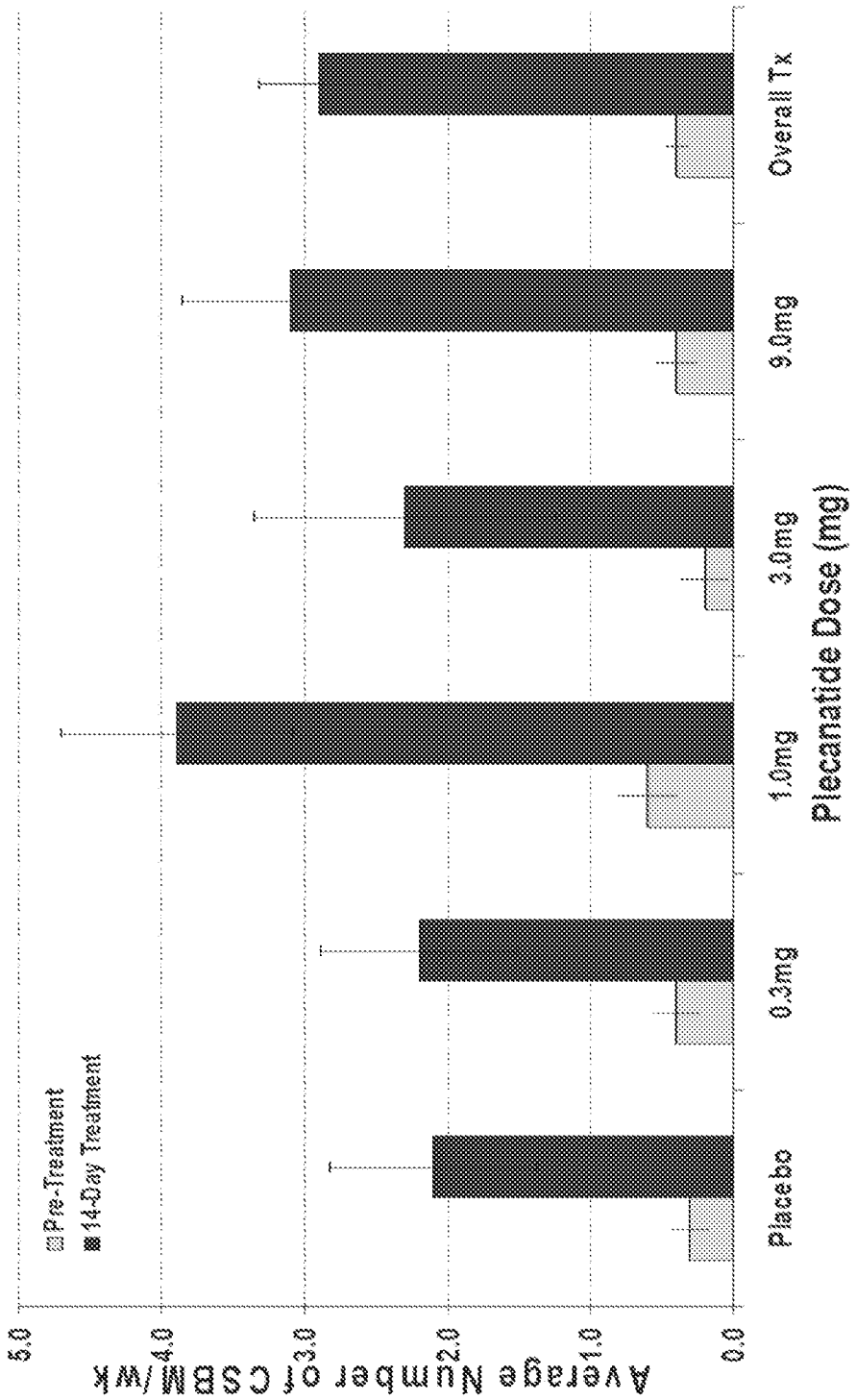
Average Number of CSBM/wk
5.0
4.0
3.0
2.0
1.0
0.0
Pre-Treatment
14-Day Treatment
Placebo
0.3mg
1.0mg
3.0mg
9.0mg
Overall Tx
Plecanatide Dose (mg)

Fig. 3

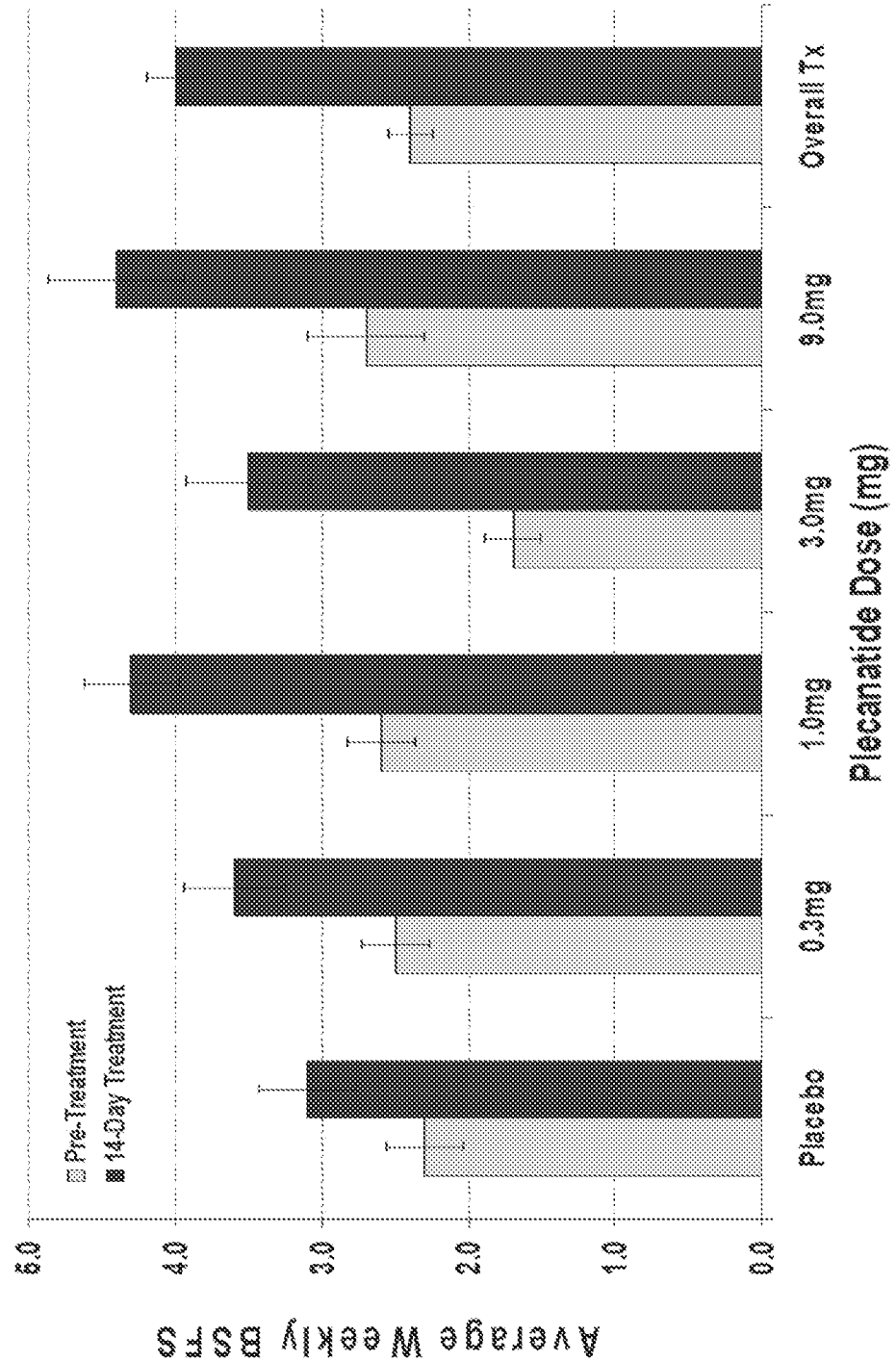
Average Weekly BSFS
6.0
4.0
3.0
2.0
1.0
0.0
Pre-Treatment
14-Day Treatment
Placebo
0.3mg
1.0mg
3.0mg
9.0mg
Overall Tx
Plecanatide Dose (mg)

Fig. 4

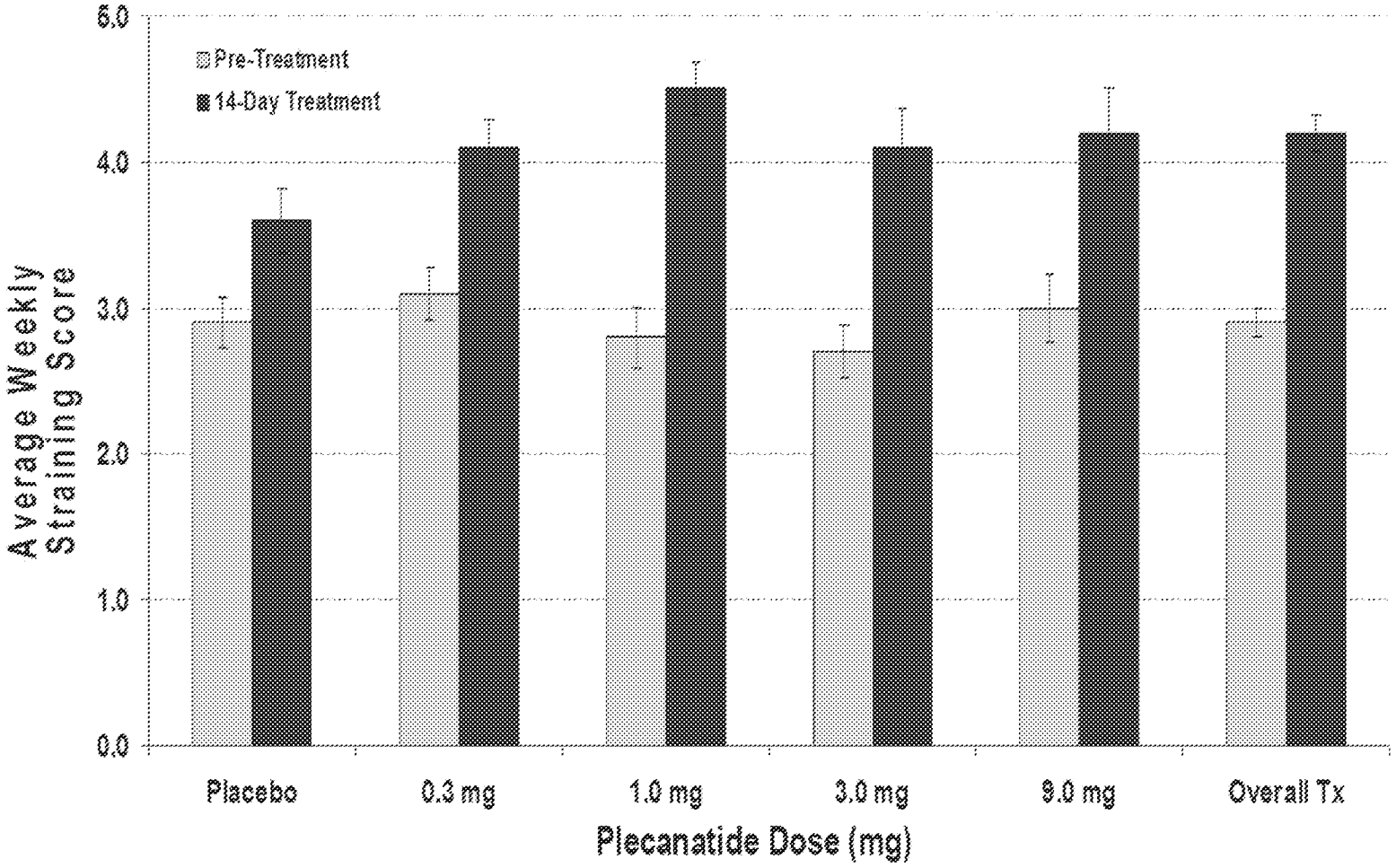
6.0
4.0
3.0
2.0
1.0
0.0
Pre-Treatment
14-Day Treatment
Average Weekly Straining Score
Placebo
0.3 mg
1.0 mg
3.0 mg
9.0 mg
Overall Tx
Plecanatide Dose (mg)

Fig. 5

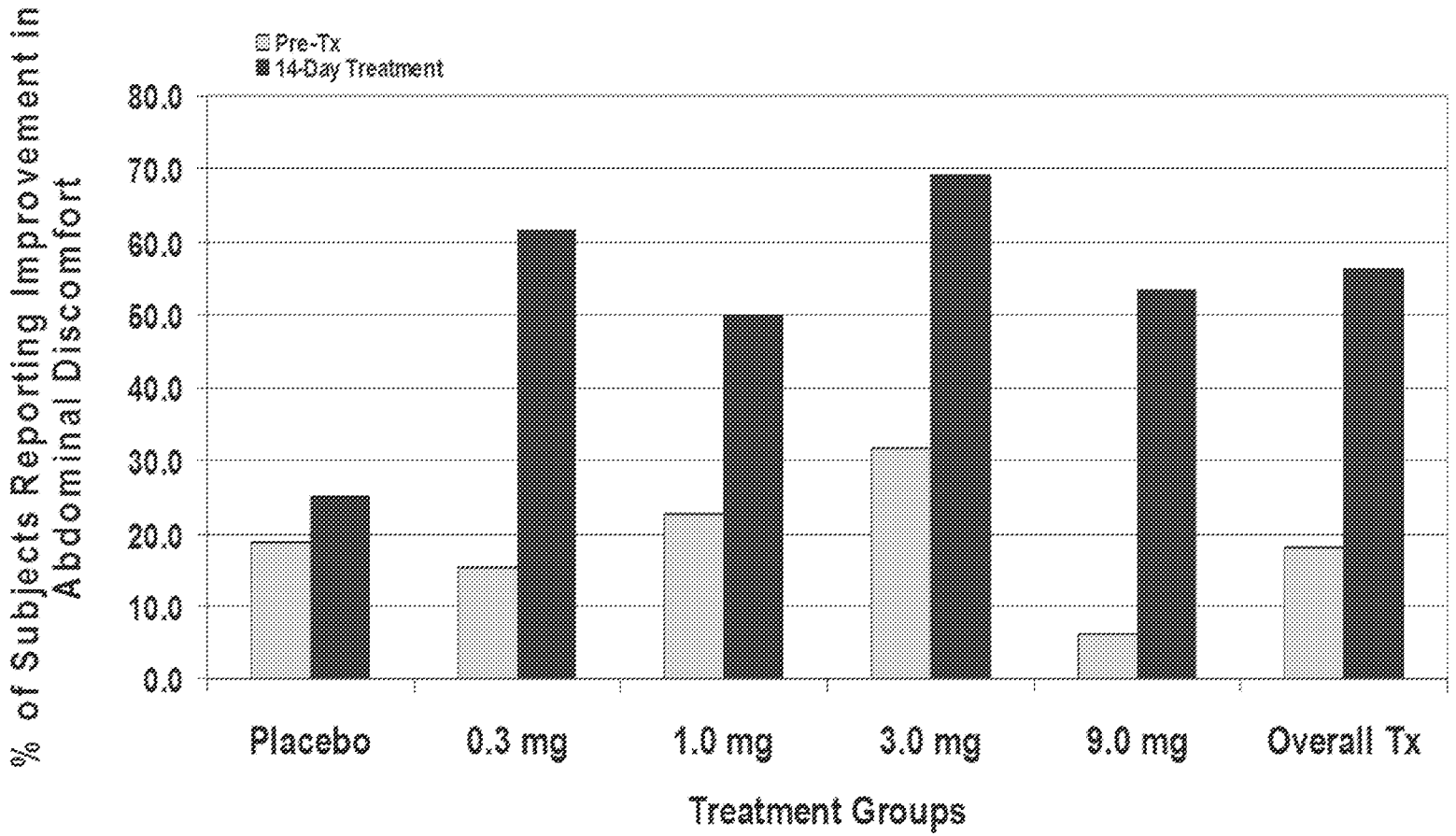
% of Subjects Reporting Improvement in Abdominal Discomfort
Pre-Tx
14-Day Treatment
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Placebo
0.3 mg
1.0 mg
3.0 mg
9.0 mg
Overall Tx
Treatment Groups

Fig. 6

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [x] The attached application, or
- [ ] United States application or PCT international application number _____

  filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Stephen Comiskey Date (Optional): 2/10/2015

Signature: S. Comiskey

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
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I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Rong Feng Date (Optional): 10 Feb 2015

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
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PTO/AIA/01 (06-12)
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LEGAL NAME OF INVENTOR

Inventor: John Foss Date (Optional): 09 Feb 2015

Signature: John Foss

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [x] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Kunwar Shailubhai Date (Optional): 02/10/2015

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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<222> (16)..(16)

<223> wherein x is 3-(2-naphthyl)alanine

<220>
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<223> wherein x is a D-amino acid

<400> 27

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Xaa
1 5 10 15

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<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MOD_RES
<222> (8)..(8)
<223> wherein the x is a 2-aminoisobutyric acid, Aib

<220>
<221> MOD_RES
<222> (10)..(10)
<223> wherein the x is a 2-aminoisobutyric acid, Aib

<220>
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<223> wherein LEU is a D-amino acid

<400> 28

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<220>
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<222> (15)..(15)
<223> wherein x at position 15 is ornithine

<220>
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<223> wherein x is an ornithine, Orn

<220>
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

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<221> MISC_FEATURE
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<220>
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<220>
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<223> wher

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/467,648	03/23/2017		930	SYPA-009/C04US	17	2

CONFIRMATION NO. 2133

FILING RECEIPT

58249
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

OC000000090532018

Date Mailed: 04/11/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Stephen COMISKEY, Doylestown, PA;
Rong FENG, Langhorne, PA;
John FOSS, Doylestown, PA;
Kunwar SHAILUBHAI, Audubon, PA;

Applicant(s)

SYNERGY PHARMACEUTICALS, INC., New York, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 14/845,644 09/04/2015 PAT 9610321
which is a CON of 14/661,299 03/18/2015 ABN
which is a CON of 13/421,769 03/15/2012 PAT 9616097
which is a CIP of PCT/US2011/051805 09/15/2011
which claims benefit of 61/383,156 09/15/2010
and claims benefit of 61/387,636 09/29/2010
and claims benefit of 61/392,186 10/12/2010

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: No

Permission to Access Search Results: No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 04/10/2017
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/467,648**
Projected Publication Date: 07/20/2017
Non-Publication Request: No
Early Publication Request: No
**** SMALL ENTITY ****
Title

FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/467,648

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	17 minus 20 =	*	x 40 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			200			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	930		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
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Application Number	15/467,648
Filing Date	03/23/2017
First Named Inventor	Stephen COMISKEY
Title	FORMULATIONS OF GUANYLATE CYCLASE C AND METHODS OF USE
Art Unit	1676
Examiner Name	Jai-Hai Lee
Attorney Docket Number	SYPA-009/C04US

SIGNATURE of Applicant or Patent Practitioner

Signature	/Cynthia Kozakiewicz/	Date (Optional)	
Name	Cynthia Kozakiewicz	Registration Number	42764
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

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This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

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58249

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☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

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Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

SYNERGY PHARMACEUTICALS INC.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	Oct. 6, 2014
Name	Gary S. Jacob, Ph.D.		
Title	President and Chief Executive Officer		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

Electronic Acknowledgement Receipt

EFS ID:	29785228
Application Number:	15467648
International Application Number:	
Confirmation Number:	2133
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Cynthia A. Kozakiewicz/peg waters
Filer Authorized By:	Cynthia A. Kozakiewicz
Attorney Docket Number:	SYPA-009/C04US
Receipt Date:	14-JUL-2017
Filing Date:	23-MAR-2017
Time Stamp:	13:08:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	SYPA-009_C04US_POA.PDF	405012 16ff0cf0b1135ec2af8b3b413f3782d48067c8b2	no	2

Warnings:

Information:	
Total Files Size (in bytes):	405012

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/467,648	03/23/2017	Stephen COMISKEY	SYPA-009/C04US

CONFIRMATION NO. 2133

58249
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

PUBLICATION NOTICE

OC00000092908275

Title:FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

Publication No.US-2017-0202904-A1
Publication Date:07/20/2017

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/467,648	03/23/2017	Stephen COMISKEY	SYPA-009/C04US

CONFIRMATION NO. 2133

POA ACCEPTANCE LETTER

58249
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

OC000000092933999

Date Mailed: 07/24/2017

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/14/2017.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/vnguyen/

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/25 PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	15467648
Filing Date	23-Mar-2017
First Named Inventor	Stephen COMISKEY
Attorney Docket Number	SYPA-009/C04US
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Synergy Pharmaceuticals, Inc.	100 %

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

15467631 filed on 03/23/2017

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

9616097

9610321

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

(●) Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

( ) I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

(●) Small Entity

( ) Micro Entity

( ) Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

(●) An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 42764

( ) A sole inventor

( ) A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

( ) A joint inventor; all of whom are signing this request

Signature	/Cynthia Kozakiewicz/
Name	Cynthia Kozakiewicz 0214

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	15467648
Filing Date:	23-Mar-2017
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Filer:	Cynthia A. Kozakiewicz/peg waters
Attorney Docket Number:	SYPA-009/C04US

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	2814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 15467648

Filing Date: 23-Mar-2017

Applicant/Patent under Reexamination: COMISKEY

Electronic Terminal Disclaimer filed on July 25, 2017

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	29882585
Application Number:	15467648
International Application Number:	
Confirmation Number:	2133
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Cynthia A. Kozakiewicz/peg waters
Filer Authorized By:	Cynthia A. Kozakiewicz
Attorney Docket Number:	SYPA-009/C04US
Receipt Date:	25-JUL-2017
Filing Date:	23-MAR-2017
Time Stamp:	14:28:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	072617INTEFSW00000808501283
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	36306 7383a7ec017ae9919b038f70b6acac26c04a32de	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30707 c457115a7d1b46acfe783e482f81249dea7bd22d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	67013		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

58249 7590 08/14/2017

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER
LEE, JIA-HAI

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 08/14/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/467,648	03/23/2017	Stephen COMISKEY	SYPA-009/C04US	2133

TITLE OF INVENTION: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	11/14/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

58249 7590 08/14/2017
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/467,648	03/23/2017	Stephen COMISKEY	SYPA-009/C04US	2133

TITLE OF INVENTION: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	11/14/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEE, JIA-HAI	1676	424-451000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/467,648	03/23/2017	Stephen COMISKEY	SYPA-009/C04US	2133

58249 7590 08/14/2017

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1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER	
LEE, JIA-HAI	

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 08/14/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/467,648	Applicant(s) COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *03/23/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-16*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20170731* .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SATYANARAYANA R GUDIBANDE/
Primary Examiner, Art Unit 1676

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

EXAMINER'S COMMENT

Applicant filed terminal disclaimers against the two patents US 9,610,321 B2 and US 9,616,097 B2. A third terminal disclaimer was filed for the copending application 15/467,631.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

The closest prior art reference Shailubhai et al. (Digestive Disease Week. San Diego: 2008) taught the use of a per unit dose of a [4, 12; 7, 15] bicyclic peptide consisting of SEQ ID NO: 1 (named SP-304) in a clinical trial, but the reference did not teach or suggest the composition further comprising an inert low moisture carrier and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91 % after storage for at least three months as claimed.

The other closest reference Shailubhai et al. (WO 2008/151257 A2) suggest the use of SP-304 to treat gastrointestinal disorders comprising irritable bowel syndrome (IBS) and constipation (p5, line 8-21). Shailubhai et al. further suggest the oral composition comprising a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic

acid, Primogel, or corn starch and/or a lubricant such as magnesium stearate or Sterotes (p41, line 19-30). However, Shailubhai et al. did not teach the composition consisting of SP-304, an inert low moisture carrier and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91 % after storage for at least three months as claimed.

Since applicant filed terminal disclaimers against the previously issued patents US 9,610,321B2 and US 9,616,097 B2 as well as the co-pending application No. 15/467,631, this instant application is allowable.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JIA-HAI LEE whose telephone number is (571)270-1691. The examiner can normally be reached on Mon-Fri from 9:00 A.M. to 5:30 P.M..

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Karlheinz R. Skowronek can be reached on 571-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-

273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. L./
Examiner, Art Unit 1676

31-July-2017

/SATYANARAYANA R GUDIBANDE/
Primary Examiner, Art Unit 1676

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	15/467,648	COMISKEY ET AL.	
	Examiner	Art Unit	
	JIA-HAI LEE	1676	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JIA-HAI LEE*. (3)_____.

(2) *Cynthia Kozakiewicz*. (4)_____.

Date of Interview: *14 July 2017*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☒ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: *US 9,610,321B2 and US 9,616,097 B2*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The agreement was reached. Applicant will file terminal disclaimers against the two issued patents US 9,610,321 and US 9,616,097 to place this instant application in condition for allowance. Applicant also filed a third terminal disclaimer for the other co-pending application 15/467,631.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/J. L./ Examiner, Art Unit 1676	

Notice of References Cited	Application/Control No. 15/467,648	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-9,610,321 B2	04-2017	Comiskey; Stephen	A61K9/1623	1/1
*	B	US-9,616,097 B2	04-2017	Comiskey; Stephen	A61K9/1623	1/1
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO2008151257A2	12-2008	US	Shailubhai et al.	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Shailubhai, K.; Gerson, W.; Talluto, C.; Jacob, G. Digestive Disease Week. San Diego: 2008. A randomized, double-blind, placebo-controlled, single-, ascending-, oral-dose safety, tolerability and pharmacokinetic study of SP-304 in healthy adult human male and female volunteers.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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(54) **Title:** AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS

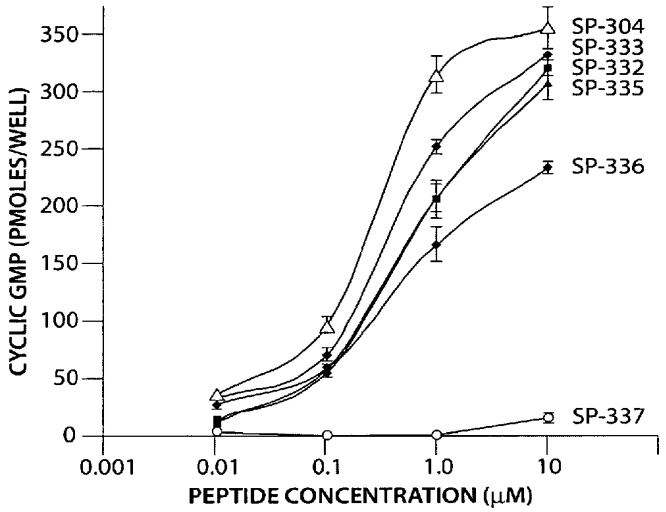

Fig. 5

(57) **Abstract:** The invention provides novel guanylate cyclase-C agonist peptides and their use in the treatment of human diseases including gastrointestinal disorders, inflammation or cancer (e.g., a gastrointestinal cancer). The peptides can be administered either alone or in combination with an inhibitor of cGMP-dependent phosphodiesterase. The gastrointestinal disorder may be classified as either irritable bowel syndrome, constipation, or excessive acidity etc. The gastrointestinal disease may be classified as either inflammatory bowel disease or other GI condition, including Crohn's disease and ulcerative colitis, and cancer.

WO 2008/151257 A2

AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 60/933,194 filed on June 4, 2007, the contents of which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to the therapeutic use of guanylate cyclase C (GC-C) agonists as a means for enhancing the intracellular production of cGMP. The agonists may be used either alone or in combination with inhibitors of cGMP-specific phosphodiesterase to prevent or treat inflammation, cancer and other disorders, particularly of the gastrointestinal tract and the lung.

BACKGROUND OF THE INVENTION

Uroguanylin, guanylin and bacterial ST peptides are structurally related peptides that bind to a guanylate cyclase receptor and stimulate intracellular production of cyclic guanosine monophosphate (cGMP) (1-6). This results in the activation of the cystic fibrosis transmembrane conductance regulator (CFTR), an apical membrane channel for efflux of chloride from enterocytes lining the intestinal tract (1-6). Activation of CFTR and the subsequent enhancement of transepithelial secretion of chloride lead to stimulation of sodium and water secretion into the intestinal lumen. Therefore, by serving as paracrine regulators of CFTR activity, cGMP receptor agonists regulate fluid and electrolyte transport in the GI tract (1-6; US patent 5,489,670). Thus, the cGMP-mediated activation of CFTR and the downstream signaling plays an important role in normal functioning of gut physiology. Therefore, any abnormality in this process could potentially lead to gastrointestinal disorders such as irritable bowel syndrome, inflammatory bowel disease, excessive acidity and cancer (25, 26).

The process of epithelial renewal involves the proliferation, migration, differentiation, senescence, and eventual loss of GI cells in the lumen (7, 8). The GI mucosa can be divided into three distinct zones based on the proliferation index of epithelial cells. One of these

zones, the proliferative zone, consists of undifferentiated stem cells responsible for providing a constant source of new cells. The stem cells migrate upward toward the lumen to which they are extruded. As they migrate, the cells lose their capacity to divide and become differentiated for carrying out specialized functions of the GI mucosa (9). Renewal of GI mucosa is very rapid with complete turnover occurring within a 24-48 hour period (9). During this process mutated and unwanted cells are replenished with new cells. Hence, homeostasis of the GI mucosa is regulated by continual maintenance of the balance between proliferation and apoptotic rates (8).

The rates of cell proliferation and apoptosis in the gut epithelium can be increased or decreased in a wide variety of different circumstances, *e.g.*, in response to physiological stimuli such as aging, inflammatory signals, hormones, peptides, growth factors, chemicals and dietary habits. In addition, an enhanced proliferation rate is frequently associated with a reduction in turnover time and an expansion of the proliferative zone (10). The proliferation index has been observed to be much higher in pathological cases of ulcerative colitis and other GI disorders (11). Thus, intestinal hyperplasia is the major promoter of gastrointestinal inflammation and carcinogenesis.

In addition to a role for uroguanylin and guanylin as modulators of intestinal fluid and ion secretion, these peptides may also be involved in the continual renewal of GI mucosa by maintaining the balance between proliferation and apoptosis in cells lining GI mucosa. Therefore, any disruption in this renewal process, due to reduced production of uroguanylin and/or guanylin can lead to GI inflammation and cancer (25, 26). This is consistent with previously published data in WO 01/25266, which suggest a peptide with the active domain of uroguanylin may function as an inhibitor of polyp development in the colon and may constitute a treatment of colon cancer. However, recent data also suggest that uroguanylin also binds to a currently unknown receptor, which is distinct from GC-C receptor (3,4). Knockout mice lacking this guanylate cyclase receptor show resistance to ST peptides in the intestine, but effects of uroguanylin and ST peptides are not disturbed in the kidney *in vivo* (3). These results were further supported by the fact that membrane depolarization induced by guanylin was blocked by genistein, a tyrosine kinase inhibitor, whereas hyperpolarization induced by uroguanylin was not effected (12, 13). Thus, it is not clear if the anti-colon cancer and anti-inflammatory activities of uroguanylin and its analogs are mediated through binding to one or both of these receptors.

Inflammatory bowel disease is a general name given to a group of disorders that cause intestines to become inflamed, characterized by red and swollen tissue. Gastrointestinal (GI) inflammation can be a chronic condition and often leads to GI cancer (14). Examples of such inflammatory bowel diseases (IBD) include Crohn's disease and ulcerative colitis (UC). It is estimated that as many as 1,000,000 Americans are afflicted with IBD, with male and female patients appearing to be equally affected. Most cases are diagnosed before age 30, but the disease can occur in the sixth, seventh, and later decades of life.

Crohn's disease is a serious inflammatory disease that predominantly effects ileum and colon, but can also occur in other sections of the GI tract, whereas UC is exclusively an inflammatory disease of the colon, the large intestine (15). Unlike Crohn's disease, in which all layers of the intestine are involved, and in which there can be normal healthy bowel in between patches of diseased bowel, UC affects only the innermost lining (mucosa) of the colon in a continuous manner (16). Depending on which portion of the GI tract is involved, Crohn's disease may be referred to as ileitis, regional enteritis, colitis, etc. Crohn's disease and UC differ from spastic colon or irritable bowel syndrome, which are motility disorders of the GI tract.

While the precise cause of IBD is not known, it is believed that the disruption of the process of continual renewal of GI mucosa may be involved in disease (17,18). The renewal process of the GI lining is an efficient and dynamic process involving the continual proliferation and replenishment of unwanted damaged cells. Proliferation rates of cells lining the GI mucosa are very high, second only to the hematopoietic system. Thus, the balance between proliferation and apoptosis is important to the maintenance of the homeostasis of the GI mucosa (19,20).

GI homeostasis depends on both proliferation and programmed cellular death (apoptosis) of epithelial cells lining the gut mucosa. Hence, cells are continually lost from the villus into the lumen of the gut and are replenished at a substantially equal rate by the proliferation of cells in the crypts, followed by their upward movement to the villus. It has become increasingly apparent that the control of cell death is an equally, if not more, important regulator of cell number and proliferation index (19,20). Reduced rates of apoptosis are often associated with abnormal growth, inflammation, and neoplastic transformation. Thus, both decreased proliferation and/or increased cell death may reduce cell number, whereas increased proliferation and/or reduced cell death may increase the

proliferation index of intestinal tissue (20), which may lead to GI inflammatory diseases and cancer.

Uroguanylin and guanylin peptides also appear to promote apoptosis by controlling cellular ion flux. Alterations in apoptosis have been associated with tumor progression to the metastatic phenotype. While a primary gastrointestinal (GI) cancer is limited to the small intestine, colon, and rectum, it may metastasize and spread to such localities as bone, lymph nodes, liver, lung, peritoneum, ovaries, and brain. By enhancing the efflux of K+ and influx of Ca++, uroguanylin and related peptides may promote the death of transformed cells and thereby inhibit metastasis

Irritable bowel syndrome (IBS) and chronic idiopathic constipation are pathological conditions that can cause a great deal of intestinal discomfort and distress but unlike the IBD diseases such as ulcerative colitis and Crohn's disease, IBS does not cause the serious inflammation or changes in bowel tissue and it is not thought to increase the risk of colorectal cancer. In the past, inflammatory bowel disease (IBD), celiac disease and irritable bowel syndrome (IBS) were regarded as completely separate disorders. Now, with the description of inflammation, albeit low-grade, in IBS, and of symptom overlap between IBS and celiac disease, this contention has come under question. Acute bacterial gastroenteritis is the strongest risk factor identified to date for the subsequent development of postinfective irritable bowel syndrome. Clinical risk factors include prolonged acute illness and the absence of vomiting. A genetically determined susceptibility to inflammatory stimuli may also be a risk factor for irritable bowel syndrome. The underlying pathophysiology indicates increased intestinal permeability and low-grade inflammation, as well as altered motility and visceral sensitivity (27). Serotonin (5-hydroxytryptamine [5-HT]) is a key modulator of gut function and is known to play a major role in pathophysiology of IBS. It has been shown that the activity of 5-HT is regulated by cGMP (28). Therefore, based on this observation as well as other effects of cGMP, we believe that GC-C agonists will be useful in the treatment of IBS.

Given the prevalence of inflammatory conditions in Western societies and the attendant risk of developing cancerous lesions from inflamed tissue, particularly intestinal tissue, a need exists to improve the treatment options for inflammatory conditions, particularly of the gastrointestinal tract.

SUMMARY OF THE INVENTION

The present invention is based upon the development of agonists of guanylate cyclase receptor. The agonists are analogs of uroguanylin and bacterial ST peptides and have superior properties such as for example high resistance to degradation at the N-terminus and C-terminus from carboxypeptidases and/or by other proteolytic enzymes present in the stimulated human intestinal juices and human gastric juices.

The peptides of the invention may be used to treat any condition that responds to enhanced intracellular levels of cGMP. Intracellular levels of cGMP can be increased by enhancing intracellular production of cGMP and/or by inhibition of its degradation by cGMP-specific phosphodiesterases. Among the specific conditions that can be treated or prevented are gastrointestinal disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, increasing gastrointestinal motility and obesity. Gastointestinal disorders include for example, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD), ileus inflammation (e.g., post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (e.g., constipation associated with use of medications such as opioids, osteoarthritis drugs , osteoporosis drugs; post surigical constipation, constipation associated with neuropathic disorders. Inflammatory disorders include tissue and organ inflammation such as kidney inflammation (e.g., nephritis), gastrointestinal system inflammation (e.g., Crohn's disease and ulcerative colitis); pancreatic inflammation (e.g., pancreatis), lung inflammation (e.g., bronchitis or asthma) or skin inflammation (e.g., psoriasis, eczema) . Lung Disorders include for example chronic obstructive pulmonary disease (COPD), and fibrosis. Cancer includes tissue and organ carcinogenesis including metatases such as for example gastrointestinal cancer, (e.g., gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (e.g., melanoma); oral cancer; urinary tract cancer (e.g. bladder cancer or kidney cancer); blood cancer (e.g. myeloma or leukemia) or prostate cancer. Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high tryglycerides. Liver disorders include for example cirrhosis and fibrosis. In addition, GC-C agonist may also be useful to facilitate liver

regeneration in liver transplant patients. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (e.g., periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include for example benign prostatic hyperplasia (BPH). Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

In one aspect, the present invention is directed to a peptide consisting essentially of the amino acid sequence of, SEQ ID NOs: 2-54 and 57-98 and to therapeutic compositions which contain these peptides. Prefered peptides include SEQ ID NO: 8, 9, 10, 58 and 59. The term "consisting essentially of" includes peptides that are identical to a recited sequence identification number and other sequences that do not differ substantially in terms of either structure or function. For the purpose of the present application, a peptide differs substantially if its structure varies by more than three amino acids from a peptide of SEQ ID NOs 2-54 and 57-98 or if its activation of cellular cGMP production is reduced by more than 50% compared to a control peptide such as SEQ ID NO:1, 55 or 56. Preferably, substantially similar peptides should differ by no more than two amino acids and not differ by more than about 25% with respect to activating cGMP production. The instant peptide sequences comprise at least 12 amino acid residues, preferably between 12 and 26 amino acids in length.

The peptides may be in a pharmaceutical composition in unit dose form, together with one or more pharmaceutically acceptable carrier, excipients or diluents. The term "unit dose form" refers to a single drug delivery entity, e.g., a tablet, capsule, solution or inhalation formulation. The amount of peptide present should be sufficient to have a positive therapeutic effect when administered to a patient (typically, between 100 μg and 3 g). What constitutes a "positive therapeutic effect" will depend upon the particular condition being treated and will include any significant improvement in a condition readily recognized by one of skill in the art. For example, it may constitute a reduction in inflammation, shrinkage of polyps or tumors, a reduction in metastatic lesions, etc.

In yet another aspect, an invention provides administering to said patient an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said guanylate cyclase receptor agonist. The cGMP-PDE inhibitor include for example suldinac sulfone, zaprinast, and motapizone, vardenifil, and sildenafil. In

addition, GC-C agonist peptides may be used in combination with inhibitors of cyclic nucleotide transporters.

Optionally, anti-inflammatory agents are also administered. Anti-inflammatory agents include for example steroids and non-steroidal anti-inflammatory drugs (NSAIDS).

Other features and advantages of the invention will be apparent from and are encompassed by the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A is a bar chart showing the biological activity of SP-304 after incubation with simulated gastric fluid (SGF) for times as indicated. The biological activity of SP-304 was determined by measuring its ability to stimulate cGMP synthesis in T84 cells. Following the incubations, samples were used for their abilities to stimulate cGMP synthesis in T84 cells. The cGMP stimulation activity in sample at 0 min of incubation with SGF was taken as 100%. The activities in samples from other times of incubations with SGF were calculated as percentage of the activity in the sample at 0 min. The data is average of triplicates ± SD

Figure 1B is a schematic representation of the results of HPLC chromatographic analyses of SP-304 samples after incubation with SGF at indicated times. The major peak of SP-304 did not change following incubation with SGF, indicating that the peptide was resistant to SGF digestion. The arrows indicate the elution position of SP-304.

Figure 2A is a bar chart showing Cyclic GMP synthesis in T84 cells by SP304 samples after incubation with simulated intestinal fluid (SIF) for the indicated times. Following the incubations, samples were used for their abilities to stimulate cGMP synthesis in T84 cells. The cGMP stimulation activity in sample at 0 min of incubation with SIF was taken as 100%. The activities in samples from other times of incubations with SIF were calculated as percentage of the activity in the sample at 0 min. The data is average of triplicates ± SD

Figure 2B is a schematic representation of the results of HPLC chromatographic analyses of SP304 samples after incubation with (A) heat inactivated SIF for 300 min or with (B) SIF for 120 min. The incubation with SIF completely converted SP-304 into another peptide eluting at 9.4 min, as indicated by *. Arrows indicate the position of SP-304.

Figure 3 is a schematic representation of the possible degradation products of SP-304.

Figure 4 shows stimulation of cGMP synthesis in T84 cells by the truncated peptides of SP-304. Thus, SP-338 has the same peptide sequence as SP-304 except that it lacks Leu at the C-terminus. Similarly, SP-327, SP-329 and SP-331 have Leu at their C-termini deleted relative to their corresponding parents, SP-326, SP-328 and SP-330. Peptides were evaluated for their abilities to stimulate cGMP synthesis in T84 cells. The results are expressed as an average of duplicates.

Figure 5 shows stimulation of cGMP synthesis in T84 cells by SP-304 and similar peptides. Cells were exposed to peptide analogs for 30 min and cell lysates were used to determine intracellular cGMP levels. Results are expressed as an average of triplicates ± SD.

Figure 6 shows stimulation of cGMP synthesis in T84 cells by SP-339 and other peptides. T84 Cells were exposed to the indicated peptide for 30 min and cell lysates were used to determine intracellular cGMP levels. Results are expressed as an average of triplicates ± SD.

Figure 7A shows stability of SP-333 against digestion with simulated intestinal fluid (SIF) for indicated times. The control sample marked as C120 was produced by incubating peptides with heat inactivated SIF. Samples from the incubations were removed and heated at 95°C for 5 min to inactivate digestive enzymes and then used to stimulate cyclic GMP synthesis in T84 cells. The cGMP stimulation activity at 0 min was taken as 100% in each set. The data is average of triplicates ± SD.

Figure 7B shows stability of SP-332 against digestion with simulated intestinal fluid (SIF) for indicated times. The control sample marked as C120 was produced by incubating peptides with heat inactivated SIF. Samples from the digestions were removed and heated at 95°C for 5 min to inactivate digestive enzymes and then used to stimulate cyclic GMP synthesis in T84 cells. The cGMP stimulation activity at 0 min was taken as 100% in each set. The data is average of triplicates ± SD.

Figure 7C shows stability of SP-304 against digestion with simulated intestinal fluid (SIF) for indicated times. The control samples marked as C0 and C60 were produced by incubating peptides with heat inactivated SIF. Samples from the digestions were removed and heated at 95°C for 5 min to inactivate digestive enzymes and then used to stimulate cyclic GMP synthesis in T84 cells. The cGMP stimulation activity at 0 min was taken as 100% in each set. The data is average of 3 determinations ± SD.

Figure 7D shows HPLC analysis of samples of SP-304 at 0 and 60 minutes following incubation with SIF. Arrow indicates the elution position of SP-304 peptide. The data clearly shows that the SP-304 peak eluting at 14.3 min completely vanished and two new peaks emerged at 7.4 and 10.3 minutes. These new peptide peaks represent the possible degradation products of SP-304.

Figure 7E shows HPLC analysis of samples of SP-332 at 0 and 120 minutes following incubation with SIF. Arrow indicates the elution position of SP-332 peptide. The data shows that the peptide SP-332 eluting at 14.8 minutes was not changed following incubation with SIF, suggesting that SP-332 is not sensitive to proteolysis by proteases present in SIF.

Figure 7F shows HPLC analysis of samples of SP-333 at 0 and 120 minutes following incubation with SIF. Arrows indicate the elution position of SP-333. The data show that peptide SP-333, eluting at 14.8 minutes, was not changed following incubation with SIF, suggesting that SP-333 is not sensitive to proteolysis by proteases present in SIF during the 120 minute incubation period.

Figure 8 shows stimulation of cGMP synthesis in T84 cells by the peggylated analogs of SP-333. T84 cells were exposed to the indicated peptides for 30 min and cell lysates were used to determine intracellular cGMP levels. Results are expressed as an average of triplicates ± SD.

Figure 9 shows stimulation of cGMP synthesis in T84 cells by SP-304 (0.1 μM) either alone or in combination with the phosphodiesterase (PDE) inhibitors Sulindac Sulfone (100 μM) or Zaprinast (100 μM). T84 cells were exposed to various treatments, as indicated, for 30 min and the cell lysates were used to determine the intracellular cGMP levels. Results are expressed as an average of duplicates.

Figure 10 shows stimulation of cGMP synthesis in T84 cells by SP-304 (0.1 or 1.0 μM) either alone or in combination with incremental concentrations of phosphodiesterase (PDE) inhibitors, as indicated. T84 cells were exposed to various treatments, as indicated, for 30 min and the cell lysates were used to determine the intracellular cGMP levels. Results are expressed as an average of duplicates.

Figure 11 shows stimulation of cGMP synthesis in T84 by SP-333 (0.1 or 1.0 μM) either alone or in combination with incremental concentrations Zaprinast, as indicated. T84 cells

were exposed to various treatments, as indicated, for 30 min and the cell lysates were used to determine the intracellular cGMP levels. Results are expressed as an average of duplicates.

Figure 12 shows stimulation of cGMP synthesis in T84 by SP-333 (0.1 μM) either alone or in combination with incremental concentrations Sulindac Sulfone, as indicated. T84 cells were exposed to various treatments, as indicated, for 30 min and the cell lysates were used to determine the intracellular cGMP levels. Results are expressed as an average of duplicates.

Figure 13 shows a schematic of the mainatance of intracellular concentrations of cGMP levels . The intracellular levels of cGMP can be maintained by stimulating its synthesis via the activation of GC-C and by inhibiting its degradation by cGMP-PDE. Thus, a combination of a GC-C agonist with an inhibitor of PDE may produce a synergistic effect to enhance levels of cGMP in tissues and organs.

DETAILED DESCRIPTION

The present invention is based upon the development of agonists of guanylate cyclase-C (GC-C). The agonists are analogs of uroguanylin and bacterial ST peptides and have superior properties such as for example high resistance to degradation at the N-terminus and C-terminus from carboxypeptidases and/or by other proteolytic enzymes such as those present in the stimulated human intestinal juices and human gastric juices.

The GC-C is expressed on various cells including on gastrointestinal epithelial cells, and on extra-intestinal tissues including kidney, lung, pancreas, pituitary, adrenal, developing liver, heart and male and female reproductive tissues (reviewed in Vaandrager 2002 Mol Cell Biochem 230:73-83). The GC-C is a key regulator of fluid and electrolyte balance in the intestine and kidney. In the intestine, when stimulated, the GC-C causes an increase in intestinal epithelial cGMP. This increase in cGMP causes a decrease in water and sodium absorption and an increase in chloride and potassium ion secretion, leading to changes in intestinal fluid and electrolyte transport and increased intestinal motility.

The gualylate cyclase-C agonists according to the invention include SEQ ID NO:2-54, and SEQ ID NO: 57-98 and are summarized below in Table I and Table II. The gualylate cyclase-C agonists according to the invention are collectively refered to herein as “GCRA peptides”.

Table I. GCRA peptides

Name	Position of Disulfide bonds	Structure	SEQ ID NO
SP-304	C4:C12, C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	1
SP-326	C3:C11, C6:C14	Asp^{1}-Glu^{2}-Cys^{3}-Glu^{4}-Leu^{5}-Cys^{6}-Val^{7}-Asn^{8}-Val^{9}-Ala^{10}-Cys^{11}-Thr^{12}-Gly^{13}-Cys^{14}-Leu^{15}	2
SP-327	C2:C10, C5:C13	Asp^{1}-Glu^{2}-Cys^{3}-Glu^{4}-Leu^{5}-Cys^{6}-Val^{7}-Asn^{8}-Val^{9}-Ala^{10}-Cys^{11}-Thr^{12}-Gly^{13}-Cys^{14}	3
SP-328	C2:C10, C5:C13	Glu^{1}-Cys^{2}-Glu^{3}-Leu^{4}-Cys^{5}-Val^{6}-Asn^{7}-Val^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Leu^{14}	4
SP-329	C2:C10, C5:C13	Glu^{1}-Cys^{2}-Glu^{3}-Leu^{4}-Cys^{5}-Val^{6}-Asn^{7}-Val^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}	5
SP-330	C1:C9, C4:C12	Cys^{1}-Glu^{2}-Leu^{3}-Cys^{4}-Val^{5}-Asn^{6}-Val^{7}-Ala^{8}-Cys^{9}-Thr^{10}-Gly^{11}-Cys^{12}-Leu^{13}	6
SP-331	C1:C9, C4:C12	Cys^{1}-Glu^{2}-Leu^{3}-Cys^{4}-Val^{5}-Asn^{6}-Val^{7}-Ala^{8}-Cys^{9}-Thr^{10}-Gly^{11}-Cys^{12}	7
SP332	C4:C12, C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$	8
SP--333	C4:C12, C7:C15	$dAsn^{1}$-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$	9
SP-334	C4:C12, C7:C15	$dAsn^{1}$-$dAsp^{2}$-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-$dLeu^{16}$	10

SP-335	C4:C12, C7:C15	dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	11
SP-336	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	12
SP-337	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-dLeu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	13
SP-338	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]	14
SP-342	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	15
SP-343	C4:C12, C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	16
SP-344	C4:C12, C7:C15	PEG3-dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	17
SP-347	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	18
SP-348	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	19
SP-350	C4:C12, C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	20
SP-352	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	21
SP-358	C4:C12, C7:C15	PEG3-dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	22
SP-359	C4:C12, C7:C15	PEG3-dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	23

WO 2008/151257 PCT/US2008/065824

SP-360	C4:C12, C7:C15	dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	24
SP-361	C4:C12, C7:C15	dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] -PEG3	25
SP-362	C4:C12, C7:C15	PEG3-dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	26
SP-368	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dNal[16]	27
SP-369	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-AIB[8]-Asn[9]-AIB[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	28
SP-370	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Asp[Lactam][7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Orn[15]-dLeu[16]	29
SP-371	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	30
SP-372	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	31
N1	C4:C12, C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] -PEG3	32
N2	C4:C12, C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	33
N3	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] PEG3	34
N4	C4:C12, C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] -PEG3	35
N5	C4:C12, C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	36
N6	C4:C12,	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] -PEG3	37

WO 2008/151257 PCT/US2008/065824

	C7:C15		
N7	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	38
N8	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]-PEG3	39
N9	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	40
N10	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]-PEG3	41
N11	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer[16] -PEG3	42
N12	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer[16]	43
N13	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer[16] -PEG3	44
Formula I	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Xaa[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-Xaa[16]	45
Formula II	C4:C12, C7:C15	Xaa_{n1}-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Xaa[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-Xaa_{n2}[16]	46
Formula III	4:12,7:15	Xaa_{n1}-Maa[4]-Glu[5]-Xaa[6]-Maa[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Maa[12]-Thr[13]-Gly[14]-Maa[15]- Xaa_{n2}	47
Formula IV	4:12,7:15	Xaa_{n1} - Maa[4]-Xaa[5]-Xaa[6]- Maa[7]-Xaa[8]-Xaa[9]-Xaa[10]-Xaa[11]- Maa[12]-Xaa[13]-Xaa[14]- Maa[15]-Xaa_{n2}	48
Formula V)	C4:C12, C7:C15	Asn[1]-Asp[2]-Asp[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Asn[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-Xaa[16]	49
Formula VI	C4:C12, C7:C15	dAsn[1]-Glu[2]-Glu[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-X3[8]-Asn[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-d-Xaa[16]	50
Formula VII	C4:C12, C7:C15	dAsn[1]-dGlu[2]-Asp[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Asn[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-d-Xaa[16]	51

Formula VII (NEW)	C4:C12, C7:C15	dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Asn[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-d-Xaa[16]	52
Formula VIII (NEW)	C4:C12, C7:C15	dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Tyr[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-d-Xaa[16]	53
Formula IX	C4:C12, C7:C15	dAsn[1]-dGlu[2]-dGlu[3]-Cys[4]-Xaa[5]-Xaa[6]-Cys[7]-Xaa[8]-Tyr[9]-Xaa[10]-Xaa[11]-Cys[12]-Xaa[13]-Xaa[14]-Cys[15]-d-Xaa[16]	54

Table II. GCRA Peptides

Name	Position of Disulfide bonds	Structure	SEQ ID NO:
SP-339	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu3-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Tyr[14]	55
SP-340	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]	56
SP-349	C1:C6, C2:C10, C5:13	PEG3-Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Tyr[14]-PEG3	57
SP-353	C3:C8, C4:C12,	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	58

	C7:15		
SP-354	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	59
SP-355	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-dTyr[14]	60
SP-357	C1:C6, C2:C10, C5:13	PEG3-Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Tyr[14]	61
SP-374	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	62
SP-375	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	63
SP-376	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	64
SP-377	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	65
SP-378	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	66
SP-379	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	67

SP-380	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	68
SP-381	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	69
SP-382	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	70
SP-383	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	71
SP384	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Tyr[14]-PEG3	72
N14	C1:C6, C2:C10, C5:13	PEG3-Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-PEG3	73
N15	C1:C6, C2:C10, C5:13	PEG3-Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]	74
N16	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-PEG3	75
N17	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	76

N18	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	77
N19	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	78
N20	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	79
N21	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	80
N22	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	81
N23	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	82
N24	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	83
N25	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	84
N26	C1:C6,	Cys[1]-Cys[2]-Glu3-Ser[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Tyr[14]	85

	C2:C10, C5:13		
N27	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Phe^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	86
N28	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Ser^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-	87
N29	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Phe^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}	88
N30	1:6, 2:10, 5:13	Pen^{1}-Pen^{2}-Glu3-Tyr^{4}-Pen^{5}-Pen^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Pen^{10}-Thr^{11}-Gly^{12}-Pen^{13}-Tyr^{14}	89
N31	1:6, 2:10, 5:13	Pen^{1}-Pen^{2}-Glu3-Tyr^{4}-Pen^{5}-Pen^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Pen^{10}-Thr^{11}-Gly^{12}-Pen^{13}	90
Formula X	C9:C14, C10:C18, C13:21	Xaa^{1}-Xaa^{2}-Xaa^{3}-Xaa^{4}-Xaa^{5}-Xaa^{6}- Asn^{7}- Tyr^{8}-Cys^{9}-Cys^{10}-Xaa^{11}-Tyr^{12}-Cys^{13}-Cys^{14}-Xaa^{15}-Xaa^{16}-Xaa^{17}-Cys^{18}- Xaa^{19}-Xaa^{20}-Cys^{21}-Xaa^{22}	91
Formula XI	C9:C14, C10:C18, C13:21	Xaa^{1}-Xaa^{2}-Xaa^{3}-Xaa^{4}-Xaa^{5}-Xaa^{6}-Asn^{7}- Phe^{8}-Cys^{9}-Cys^{10} -Xaa^{11}-Phe^{12}- Cys^{13}-Cys^{14}-Xaa^{15}-Xaa^{16}-Xaa^{17}-Cys^{18}- Xaa^{19}-Xaa^{20}-Cys^{21}-Xaa^{22}	92
Formula XII	C3:C8, C4:C12,	Asn^{1}- Phe^{2}-Cys^{3}-Cys^{4} - Xaa^{5}-Phe^{6}-Cys^{7}-Cys^{8} - Xaa^{9}-Xaa^{10}- Xaa^{11}-Cys^{12}- Xaa^{3}-Xaa^{14}-Cys^{15}-Xaa^{16}	93

	C7:15		
Formula XIII	3:8, 4:12, C:15	Asn^{1}- Phe^{2}-Pen^{3}-Cys^{4} - Xaa^{5}-Phe^{6}-Cys^{7}-Pen^{8} - Xaa^{9}-Xaa^{10}- Xaa^{11}-Cys12- Xaa^{13}-Xaa^{14}-Cys^{15}-Xaa^{16}	94
Formula XIV	3:8, 4:12, 7:15	Asn^{1}- Phe^{2}-Maa^{3}-Maa^{4} - Xaa^{5}-Xaa^{6}-Maa^{7}-Maa^{8} - Xaa^{9}-Xaa^{10}- Xaa^{11}-Maa^{12}- Xaa^{13}-Xaa^{14}-Maa^{15}-Xaa^{16}	95
Formula XV	1:6, 2:10, 5:13	Maa^{1}-Maa^{2}-Glu3-Xaa^{4}- Maa^{5}-Maa^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Maa^{10}-Thr^{11}-Gly^{12}-Maa^{13}-Tyr^{14}	96
Formula XVI	1:6, 2:10, 5:13	Maa^{1}-Maa^{2}-Glu3-Xaa^{4}- Maa^{5}-Maa^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Maa^{10}-Thr^{11}-Gly^{12}-Maa^{13}-	97
Formula XVII	1:6, 2:10, 5:13	Xaa_{n3}-Maa^{1}-Maa^{2}-Xaa^{3}-Xaa^{4}-Maa^{5}-Maa^{6}-Xaa^{7}-Xaa^{8}-Xaa^{9}-Maa^{10}-Xaa^{11}-Xaa^{12}-Maa^{13}-Xaa_{n2}	98

The GCRA peptides described herein bind the guanylate cyclase C (GC-C) and stimulate intracellular production of cyclic guanosine monophosphate (cGMP). Optionally, the GCRA peptides induce apoptosis. In some aspects, the GCRA peptides stimulate intracellular cGMP production at higher levels than naturally occurring GC-C agonists (*e.g.*, uroguanylin, guanylin, and ST peptides) and/or SP-304. For example, the GCRA peptides of the invention stimulate 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared to naturally occurring GC-C angonists and/or SP-304. The terms induced and stimulated are used interchangeably throughout the specification. The GCRA peptides described herein are more stable than naturally occurring GC-C agonists and/or SP-304. By more stable it is meant that the peptide degrade less and/or more slowly in simulated gastrointestinal fluid and/or simulatd intestinal fluid compared to naturally occurring GC-C angonists and/or SP-304. For example, the GCRA peptide of the invention degrade 2%, 3%, 5%, 10%, 15%, 20%, 30%, 40%, 50% , 75%, 90% or less compared to naturally occurring GC-C angonists and/or SP-304.

The GCRA peptides described herein have therapeutic value in the treatment of a wide variety of disorders and conditions including for example gastrointestinal disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, increasing gastrointestinal motility and obesity. Gastointestinal disorders include for example, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD)ileus (*e.g.*, post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (*e.g.*, constipation associated with use of medications such as opioids, osteoarthritis drugs , osteoporosis drugs; post surigical constipation, constipation associated with neuropathic disorders. Inflammatory disorders include tissue and organ inflammation such as kidney inflammation (*e.g.*, nephritis), gastrointestinal system inflammation (*e.g.*, Crohn's disease and ulcerative colitis); pancreatic inflammation (*e.g.*, pancreatis), lung inflammation (*e.g.*, bronchitis or asthma) or skin inflammation (*e.g.*, psoriasis, eczema). Lung Disorders include for example chronic obstructive pulmonary disease (COPD), and fibrosis. Cancer includes tissue and organ carcinogenesis including metatases such as for example gastrointestinal cancer, (*e.g.*, gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal

cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (*e.g.*, melanoma); oral cancer; urinary tract cancer (*e.g.* bladder cancer or kidney cancer); blood cancer (*e.g.* myeloma or leukemia) or prostate cancer. Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high tryglycerides. Liver disorders include for example cirrhosis and fibrosis. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (*e.g.*, periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include for example Benign prostatic hyperplasia (BPH). Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

As used herein, the term "guanylate cyclase C (GC-C)" refers to the class of guanylate cyclase C receptor on any cell type to which the inventive agonist peptides or natural agonists described herein bind. As used herein, "intestinal guanylate cyclase receptor" is found exclusively on epithelial cells lining the GI mucosa. Uroguanylin, guanylin, and ST peptides are expected to bind to these receptors and may induce apoptosis. The possibility that there may be different receptors for each agonist peptide is not excluded. Hence, the term refers to the class of guanylate cyclase receptors on epithelial cells lining the GI mucosa.

As used herein, the term "GCR agonist" is meant to refer to peptides and/or other compounds that bind to an intestinal guanylate cyclase C and stimulate fluid and electrolyte transport. This term also covers fragments and pro-peptides that bind to GC-C and stimulate fluid and water secretion.

As used herein, the term "substantially equivalent" is meant to refer to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without impairing the peptide's ability to bind to an intestinal guanylate cyclase receptor and stimulate fluid and electrolyte transport.

Addition of carriers (*e.g.*, phosphate-buffered saline or PBS) and other components to the composition of the present invention is well within the level of skill in this art. In addition to the compound, such compositions may contain pharmaceutically acceptable carriers and other ingredients known to facilitate administration and/or enhance uptake. Other formulations, such as microspheres, nanoparticles, liposomes, and immunologically-based systems may also be used

in accordance with the present invention. Other examples include formulations with polymers (*e.g.*, 20% w/v polyethylene glycol) or cellulose, or enteric formulations.

The present invention is based upon several concepts. The first is that there is a cGMP-dependent mechanism which regulates the balance between cellular proliferation and apoptosis and that a reduction in cGMP levels, due to a deficiency of uroguanylin/guanylin and/or due to the activation of cGMP-specific phosphodiesterases, is an early and critical step in neoplastic transformation. A second concept is that the release of arachidonic acid from membrane phospholipids, which leads to the activation of cytoplasmic phospholipase A2 (cPLA2), cyclooxygenase-2 (COX-2) and possibly 5-lipoxygenase (5-LO) during the process of inflammation, is down-regulated by a cGMP-dependent mechanism, leading to reduced levels of prostaglandins and leukotrienes, and that increasing intracellular levels of cGMP may therefore produce an anti-inflammatory response. In addition, a cGMP-dependent mechanism, is thought to be involved in the control of proinflammatory processes. Therefore, elevating intracellular levels of cGMP may be used as a means of treating and controlling gastrointestinal disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, increasing gastrointestinal motility and obesity.Gastointestinal disorders include for example, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD)ileus (e.g., post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (*e.g.*, constipation associated with use of medications such as opioids, osteoarthritis drugs, osteoporosis drugs; post surigical constipation, constipation associated with neuropathic disorders. Inflammatory disorders include tissue and organ inflammation such as kidney inflammation (*e.g.*, nephritis), gastrointestinal system inflammation (*e.g.*, Crohn's disease and ulcerative colitis); pancreatic inflammation (*e.g.*, pancreatis), lung inflammation (*e.g.*, bronchitis or asthma) or skin inflammation (e.g., psoriasis, eczema). Lung Disorders include for example COPD and fibrosis. Cancer includes tissue and organ carcinogenesis including metatases such as for example gastrointestinal cancer, (*e.g.*, gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (*e.g.*, melanoma); oral cancer; urinary tract cancer (*e.g.* bladder cancer or kidney cancer); blood cancer (*e.g.* myeloma or

leukemia) or prostate cancer. Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high tryglycerides. Liver disorders include for example cirrhosis and fibrosis. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (*e.g.*, periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include for example Benign prostatic hyperplasia (BPH). Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

Without intending to be bound by any theory, it is envisioned that ion transport across the plasma membrane may prove to be an important regulator of the balance between cell proliferation and apoptosis that will be affected by agents altering cGMP concentrations. Uroguanylin has been shown to stimulate K+ efflux, Ca++ influx and water transport in the gastrointestinal tract (3). Moreover, atrial natriuretic peptide (ANP), a peptide that also binds to a specific guanylate cyclase receptor, has also been shown to induce apoptosis in rat mesangial cells, and to induce apoptosis in cardiac myocytes by a cGMP mechanism (21-24).

Binding of the present agonists to a guanylate cyclase receptor stimulates production of cGMP. This ligand-receptor interaction, via activation of a cascade of cGMP-dependent protein kinases and CFTR, induces apoptosis in target cells. Therefore, administration of the novel peptides defined by SEQ ID NO:2-54, and SEQ ID NO: 57-98, as shown in Tables I and II, or peptides similar to uroguanylin, or guanylin or E. coli ST peptide are useful in eliminating or, at least retarding, the onset of gastrointestinal disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, increasing gastrointestinal motility and obesity.Gastointestinal disorders include for example, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD), ileus inflammation (*e.g.*, post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (*e.g.*, constipation associated with use of medications such as opioids, osteoarthritis drugs, osteoporosis drugs; post surigical constipation, constipation associated with neuropathic disorders. Inflammatory disorders include tissue and organ inflammation such as kidney

inflammation (*e.g.*, nephritis), gastrointestinal system inflammation (*e.g.*, Crohn's disease and ulcerative colitis); pancreatic inflammation (*e.g.*, pancreatis), lung inflammation (*e.g.*, bronchitis or asthma) or skin inflammation (*e.g.*, psoriasis, eczema). Lung Disorders include for example chronic obstructive pulmonary disease (COPD), and fibrosis. Cancer includes tissue and organ carcinogenesis including metatases such as for example gastrointestinal cancer, (*e.g.*, gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (*e.g.*, melanoma); oral cancer; urinary tract cancer (*e.g.* bladder cancer or kidney cancer); blood cancer (*e.g.* myeloma or leukemia) or prostate cancer. Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high tryglycerides. Liver disorders include for example cirrhosis and fibrosis. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (*e.g.*, periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include for example Benign prostatic hyperplasia (BPH). Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

Uroguanylin is a circulating peptide hormone with natriuretic activity and has been found to stimulate fluid and electrolyte transport in a manner similar to another family of heat stable enterotoxins (ST peptides) secreted by pathogenic strains of *E. coli* and other enteric bacteria that activate guanylate cyclase receptor and cause secretory diarrhea. Unlike bacterial ST peptides, the binding of uroguanylin to guanylate cyclase receptor is dependent on the physiological pH of the gut. Therefore, uroguanylin is expected to regulate fluid and electrolyte transport in a pH dependent manner and without causing severe diarrhea.

GCRA PEPTIDES

In one aspect, the invention provides a GCRA peptide. The GCRA peptides are analogues uroguanylin and bacterial ST peptide. No particular length is implied by the term "peptide". In some embodiments, the GCRA peptide is less than 25 amino acids in length, *e.g.,* less than or equal to 20, 15, 14, 13, 12, 11, 10, or 5 amino acid in length.

The GCRA peptides can be polymers of L-amino acids, D-amino acids, or a combination of both. For example, in various embodiments, the peptides are D retro-inverso peptides. The

term "retro-inverso isomer" refers to an isomer of a linear peptide in which the direction of the sequence is reversed and the chirality of each amino acid residue is inverted. *See*, *e.g.*, Jameson *et al.*, *Nature*, 368, 744-746 (1994); Brady *et al.*, Nature, 368, 692-693 (1994). The net result of combining D-enantiomers and reverse synthesis is that the positions of carbonyl and amino groups in each amide bond are exchanged, while the position of the side-chain groups at each alpha carbon is preserved. Unless specifically stated otherwise, it is presumed that any given L-amino acid sequence of the invention may be made into an D retro-inverso peptide by synthesizing a reverse of the sequence for the corresponding native L-amino acid sequence. For example a GCRA peptide includes the sequence of SEQ ID NO: SEQ ID NO:2-54, and SEQ ID NO: 57-98. In various embodiments, the GCRA peptide includes the amino acid sequence of SEQ ID NO:45-54 and SEQ ID NO:87-98 where the peptide induces cGMP production by a cell. In various embodiments the GCRA peptide of the invention includes the amino acid sequence according to Formulas I-IX (*e.g.* SEQ ID NO:45-54) with the proviso that the GCRA peptide is not SEQ ID NO:1. In further embodiments the GCRA peptide of the invention include the amino acid sequence according to Formulas X- XVII (*e.g.* SEQ ID NO:87-98) with the proviso that the GCRA peptide is not SEQ ID NO:55 or SEQ ID NO:56. By inducing cGMP production is meant that the GCRA peptide induces the production of intracellular cGMP. Intracellular cGMP is measured by methods known in the art. For example, the GCRA peptide of the invention stimulate 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared to naturally occurring GC-C angonists. Optionally, the GCRA peptides of the invention of the invention stimulate 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared SP-304 (SEQ ID NO:1). In further embodiments, the GCRA peptide stimulates apoptosis, *e.g.*, programmed cell death or activate the cystic fibrosis transmembrane conductance regulator (CFTR). In some embodimenst the GCRA peptides described herein are more stable than naturally occurring GC-C agonists and/or SP-304 (SEQ ID NO:1), SP-339 (SEQ ID NO: 55) or SP-340 (SEQ ID NO: 56). By more stable it is meant that the peptide degrade less and/or more slowly in simulated gastric fluid and/or simulated ntestinal fluid compared to naturally occurring GC-C angonists and/or SP-304. For example, the GCRA peptide of the invention degrade 2%, 3%, 5%, 10%, 15%, 20%, 30%, 40%, 50% , 75%, 90% or less compared to naturally occurring GC-C angonists and/or SP-304, SP-339 or SP-340.

As used herein PEG3, 3 PEG, is meant to denote polyethylene glycol such as include aminoethyloxy-ethyloxy-acetic acid (AeeA). As used herein, (*e.g.*, in Formulas I- XVII, SEQ ID NO:45-54 and SEQ ID NO:87-98) X_{aa} is any any natural, unnatural amino acid or amino acid analogue; M_{aa} is a Cysteine (Cys), Penicillamine (Pen) homocysteine, or 3-mercaptoproline; Xaa_{n1} is meant to denote an amino acid sequence of any any natural, unnatural amino acid or amino acid analogue that is one, two or three residues in length; Xaa_{n2} is meant to denote an amino acid sequence of any any natural, unnatural amino acid or amino acid analogue that is zero or one residue in length; and Xaa_{n3} is meant to denote an amino acid sequence of any any natural, unnatural amino acid or amino acid analogue that is zero, one, two, three, four , five or six residues in length. Additionally, any amino acid represented by Xaa, $Xaa_{n1,}$ $Xaa_{n2,\ or}$ Xaa_{n3} may be an L-amino acid, a D-amino acid, a methylated amino acid or any combination of thereof. Optionally, any GCRA peptide represented by Formulas I-VII may contain on or more polyethylene glycol residues at the the N- terminus, C-terminus or both. An exemplary polyethylene glycol include aminoethyloxy-ethyloxy-acetic acid and polymers thereof.

In some embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula I, wherein at at least one amino acid of Formula I is a D-amino acid or a methylated amino acid and/or the amino acid at position 16 is a serine. Preferably, the amino acid at position 16 of Formula I is a D-amino acid or a methylated amino acid. For example, the amino acid at position 16 of Formula I is a d-leucine or a d-serine. Optionally, one or more of the amino acids at position 1-3 of Formula I are D-amino acids or methylated amino acids or a combination of D-amino acids or methylated amino acids. For example, Asn1, Asp2 or Glu3 (or a combination thereof) of Formula I is a D-amino acids or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula I is a leucine, serine or tyrosine.

In alternative embodiments, GCRA peptides include peptides containing containing the amino acid sequence of Formula II, wherein at least one amino acid of Formula II is a D-amino acid or a methylated amino acid. Preferably, the amino acid denoted by Xaa_{n2} of Formula II is a D-amino acid or a methylated amino acid. In some embodimenst the amino acid denoted by Xaa_{n2} of Formula II is a leucine, d-leucine, serine or d-serine. Preferably, the one or more of the amino acids denoted by Xaa_{n1} of Formula II is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula II is a leucine, serine or tyrosine.

In some embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula III, wherein 1) at at least one amino acid of Formula I is a D-amino acid or a methylated amino acid and/or 2) Maa is not a cysteine. Preferably, the amino acid denoted by Xaa_{n2} of Formula III is a D-amino acid or a methylated amino acid. In some embodiments the amino acid denoted by Xaa_{n2} of Formula III is a leucine, d-leucine, serine or d-serine. Preferably, the one or more of the amino acids denoted by Xaa_{n1} of Formula III is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula III is a leucine, serine or tyrosine.

In other embodiments, GCRA peptides include peptides containing containing the amino acid sequence of Formula IV, wherein at least one amino acid of Formula IV is a D-amino acid or a methylated amino acid and/or 2) Maa is not a cysteine. Preferably, the Xaa_{n2} of Formula IV is a D-amino acid or a methylated amino acid. In some embodimenst the amino acid denoted by Xaa_{n2} of Formula IV is a leucine, d-leucine, serine or d-serine. Preferably, the one or more of the amino acids denoted by Xaa_{n1} of Formula IV is a D-amino acid or a methylated amino acid. Preferably, the amino acid denoted Xaa^6 of Formula IV is a leucine , serine or tyrosine. In further embodiments, GCRA peptides include peptides containing containing the amino acid sequence of Formula V, wherein at at least one amino acid of Formula V is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position 16 of Formula V is a D-amino acid or a methylated amino acid. For example, the amino acid at position 16 (i.e., Xaa^{16}) of Formula V is a d-leucine or a d-serine. Optionally, one or more of the amino acids at position 1-3 of Formula V are D-amino acids or methylated amino acids or a combination of D-amino acids or methylated amino acids. For example, Asn1, Asp2 or Glu3 (or a combination thereof) of Formula V is a D-amino acids or a methylated amino acid. Preferably, the amino acid denoted at Xaa^6 of Formula V is a leucine, serine or tyrosine.

In additional embodiments, GCRA peptides include peptides containing containing the amino acid sequence of Formula VI, VII, VIII, IX. Preferably, the amino acid at position 6 of Formula VI, VII, VIII, IX. is a leucine, serine or tyrosine. In some aspects the amino acid at position 16 of Formula VI, VII, VIII, IX is a leucine or a serine. Preferably, the amino acid at position 16 of Formula V is a D-amino acid or a methylated amino acid.

In prefered embodiments, the GCRA peptide is SP-332 (SEQ ID NO:8), SP-333 (SEQ ID NO:9) or SP-334 (SEQ ID NO:10).

In additional embodiments, GCRA peptides include peptides containing containing the amino acid sequence of Formula X, XI, XII, XIII, XIV, XV, XVI or XVII. Optionally, one or more amino acids of Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-amino acid or a methylated amino acid. Preferably, the amino acid at the carboxy terminus of the peptides according to Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-amino acid or a methylated amino acid. For example the the amino acid at the carboxy terminus of the peptides according to Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-tyrosine

Preferably, the amino acid denoted by Xaa^6 of Formula XIV is a tyrosine, phenyalanine or a serine. Most preferably the amino acid denoted by Xaa^6 of Formula XIV is a phenyalanine or a serine. Preferably, the amino acid denoted by Xaa^4 of Formula XV, XVI or XVII is a tyrosine, phenyalanine or a serine. Most preferably, the amino acid position Xaa^4 of Formula V, XVI or XVII is a phenyalanine or a serine.

In prefered embodiments, the GCRA peptide is SP-353 (SEQ ID NO:58) or SP-354 (SEQ ID NO:59).

In certain embodiments, one or more amino acids of the GCRA peptides can be replaced by a non-naturally occurring amino acid or a naturally or non-naturally occurring amino acid analog. There are many amino acids beyond the standard 20 (Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val). Some are naturally-occurring others are not. (*See*, for example, Hunt, The Non-Protein Amino Acids: In Chemistry and Biochemistry of the Amino Acids, Barrett, Chapman and Hall, 1985). For example, an aromatic amino acid can be replaced by 3,4-dihydroxy-L-phenylalanine, 3-iodo-L-tyrosine, triiodothyronine, L-thyroxine, phenylglycine (Phg) or nor-tyrosine (norTyr). Phg and norTyr and other amino acids including Phe and Tyr can be substituted by, *e.g.*, a halogen, -CH3, -OH, -CH2NH3, -C(O)H, -CH2CH3, - CN, -CH2CH2CH3, -SH, or another group. Any amino acid can be substituted by the D-form of the amino acid.

With regard to non-naturally occurring amino acids or naturally and non-naturally occurring amino acid analogs, a number of substitutions in the polypeptide and agonists described herein are possible alone or in combination.

For example, glutamine residues can be substituted with gamma-Hydroxy-Glu or gamma- Carboxy-Glu. Tyrosine residues can be substituted with an alpha substituted amino acid such as L-alpha-methylphenylalanine or by analogues such as: 3-Amino-Tyr; Tyr(CH3); Tyr(PO3(CH3)2); Tyr(SO3H); beta-Cyclohexyl-Ala; beta-(l-Cyclopentenyl)-Ala; beta-Cyclopentyl-Ala; beta-Cyclopropyl-Ala; beta-Quinolyl-Ala; beta-(2-Thiazolyl)-Ala; beta-(Triazole-l-yl)-Ala; beta-(2-Pyridyl)-Ala; beta-(3-Pyridyl)-Ala; Amino-Phe; Fluoro-Phe; Cyclohexyl-Gly; tBu-Gly; beta-(3-benzothienyl)-Ala; beta-(2-thienyl)-Ala; 5-Methyl-Trp; and A- Methyl-Trp. Proline residues can be substituted with homopro (L-pipecolic acid); hydroxy-Pro; 3,4-Dehydro-Pro; 4-fluoro-Pro; or alpha-methyl-Pro or an N(alpha)-C(alpha) cyclized amino acid analogues with the structure: n = 0, 1, 2, 3 Alanine residues can be substituted with alpha-substitued or N-methylated amino acid such as alpha-amino isobutyric acid (aib), L/D-alpha-ethylalanine (L/D-isovaline), L/D-methylvaline, or L/D-alpha-methylleucine or a non-natural amino acid such as beta-fluoro-Ala. Alanine can also be substituted with: n = 0, 1, 2, 3 Glycine residues can be substituted with alpha-amino isobutyric acid (aib) or L/D-alpha-ethylalanine (L/D-isovaline).

Further examples of unnatural amino acids include: an unnatural analog of tyrosine; an unnatural analogue of glutamine; an unnatural analogue of phenylalanine; an unnatural analogue of serine; an unnatural analogue of threonine; an alkyl, aryl, acyl, azido, cyano, halo, hydrazine, hydrazide, hydroxyl, alkenyl, alkynl, ether, thiol, sulfonyl, seleno, ester, thioacid, borate, boronate, phospho, phosphono, phosphine, heterocyclic, enone, imine, aldehyde, hydroxylamine, keto, or amino substituted amino acid, or any combination thereof; an amino acid with a photoactivatable cross-linker; a spin-labeled amino acid; a fluorescent amino acid; an amino acid with a novel functional group; an amino acid that covalently or noncovalently interacts with another molecule; a metal binding amino acid; an amino acid that is amidated at a site that is not naturally amidated, a metal-containing amino acid; a radioactive amino acid; a photocaged and/or photoisomerizable amino acid; a biotin or biotin-analogue containing amino acid; a glycosylated or carbohydrate modified amino acid; a keto containing amino acid; amino acids comprising polyethylene glycol or polyether; a heavy atom substituted amino acid (*e.g.*, an amino acid containing deuterium, tritium, ^{13}C, ^{15}N, or ^{18}O); a chemically cleavable or photocleavable amino acid; an amino acid with an elongated side chain; an amino acid containing a toxic group; a sugar substituted amino acid, *e.g.*, a sugar substituted serine or the

like; a carbon-linked sugar-containing amino acid; a redox-active amino acid; an α-hydroxy containing acid; an amino thio acid containing amino acid; an α, α disubstituted amino acid; a β-amino acid; a cyclic amino acid other than proline; an O-methyl-L-tyrosine; an L-3-(2-naphthyl)alanine; a 3-methyl-phenylalanine; a ρ-acetyl-L-phenylalanine; an O-4-allyl-L-tyrosine; a 4-propyl-L-tyrosine; a tri-O-acetyl-GlcNAc β -serine; an L-Dopa; a fluorinated phenylalanine; an isopropyl-L-phenylalanine; a p-azido-L-phenylalanine; a p-acyl-L-phenylalanine; a p-benzoyl-L-phenylalanine; an L-phosphoserine; a phosphonoserine; a phosphonotyrosine; a p-iodo-phenylalanine; a 4-fluorophenylglycine; a p-bromophenylalanine; a p-amino-L-phenylalanine; an isopropyl-L-phenylalanine; L-3-(2-naphthyl)alanine; D- 3-(2-naphthyl)alanine (dNal); an amino-, isopropyl-, or O-allyl-containing phenylalanine analogue; a dopa, 0-methyl-L-tyrosine; a glycosylated amino acid; a p-(propargyloxy)phenylalanine; dimethyl-Lysine; hydroxy-proline; mercaptopropionic acid; methyl-lysine; 3-nitro-tyrosine; norleucine; pyro-glutamic acid; Z (Carbobenzoxyl); ε-Acetyl-Lysine; β-alanine; aminobenzoyl derivative; aminobutyric acid (Abu); citrulline; aminohexanoic acid; aminoisobutyric acid (AIB); cyclohexylalanine; d-cyclohexylalanine; hydroxyproline; nitro-arginine; nitro-phenylalanine; nitro-tyrosine; norvaline; octahydroindole carboxylate; ornithine (Orn); penicillamine (PEN); tetrahydroisoquinoline; acetamidomethyl protected amino acids and pegylated amino acids. Further examples of unnatural amino acids and amino acid analogs can be found in U.S. 20030108885, U.S. 20030082575, US20060019347 (paragraphs 410-418) and the references cited therein. The polypeptides of the invention can include further modifications including those described in US20060019347, paragraph 589. Exempary GCRA peptides which include a n0n-naturally occurring amino acid include for example SP-368 and SP-369.

In some embodiments, an amino acid can be replaced by a naturally-occurring, non-essential amino acid, *e.g.*, taurine.

Alternatively, the GCRA peptides are cyclic peptides. GCRA cyclic peptide are prepared by methods known in the art. For example, macrocyclization is often accomplished by forming an amide bond between the peptide N- and C-termini, between a side chain and the N- or C-terminus [*e.g.*, with $K_3Fe(CN)_6$ at pH 8.5] (Samson *et al.*, *Endocrinology,* 137: 5182-5185 (1996)), or between two amino acid side chains, such as cysteine. See, *e.g.,* DeGrado, *Adv Protein Chem, 39*: 51-124 (1988). In various aspects the GCRA peptides are [4,12; 7,15] bicycles.

In some GCRA peptides one or both members of one or both pairs of Cys residues which normally form a disulfide bond can be replaced by homocysteine, penicillamine, 3-mercaptoproline (Kolodziej et al. 1996 Int J Pept Protein Res 48:274); β, β dimethylcysteine (Hunt et al. 1993 Int JPept Protein Res 42:249) or diaminopropionic acid (Smith et al. 1978 J Med Chem 2 1:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

In addition, one or more disulfide bonds can be replaced by alternative covalent cross-links, *e.g.*, an amide linkage (-CH2CH(O)NHCH 2- or -CH2NHCH(O)CH 2-), an ester linkage, a thioester linkage, a lactam bridge , a carbamoyl linkage, a urea linkage, a thiourea linkage, a phosphonate ester linkage, an alkyl linkage (-CH2CH2CH2CH2-), an alkenyl linkage(-CH 2CH=CHCH 2-), an ether linkage (-CH2CH2OCH2- or -CH2OCH2CH2-), a thioether linkage (-CH2CH2SCH2- or - CH2SCH2CH2-), an amine linkage (-CH2CH2NHCH2- or -CH2NHCH 2CH2-) or a thioamide linkage (-CH2CH(S)HNHCH 2- or -CH2NHCH(S)CH 2-). For example, Ledu et al. (Proc Nat'l Acad. Sci. 100:11263-78, 2003) describe methods for preparing lactam and amide cross-links. Exemplary GCRA peptides which include a lactam bridge include for example SP-370.

The GCRA peptides can have one or more conventional polypeptide bonds replaced by an alternative bond. Such replacements can increase the stability of the polypeptide. For example, replacement of the polypeptide bond between a residue amino terminal to an aromatic residue (*e.g.* Tyr, Phe, Trp) with an alternative bond can reduce cleavage by carboxy peptidases and may increase half-life in the digestive tract. Bonds that can replace polypeptide bonds include: a retro-inverso bond (C(O)-NH instead of NH-C(O); a reduced amide bond (NH-CH2); a thiomethylene bond (S-CH2 or CH2-S); an oxomethylene bond (0-CH 2 or CH2-O); an ethylene bond (CH2-CH2); a thioamide bond (C(S)-NH); a trans-olefine bond (CH=CH); a fiuoro substituted trans-olefme bond (CF=CH); a ketomethylene bond (C(O)-CHR or CHR-C(O) wherein R is H or CH3; and a fluoro-ketomethylene bond (C(O)-CFR or CFR-C(O) wherein R is H or F or CH3.

The GCRA peptides can be modified using standard modifications. Modifications may occur at the amino (N-), carboxy (C-) terminus, internally or a combination of any of the preceeding. In one aspect described herein, there may be more than one type of modification on

the polypeptide. Modifications include but are not limited to: acetylation, amidation, biotinylation, cinnamoylation, farnesylation, formylation, myristoylation, palmitoylation, phosphorylation (Ser, Tyr or Thr), stearoylation, succinylation, sulfurylation and cyclisation (via disulfide bridges or amide cyclisation), and modification by Cys3 or Cys5. The GCRA peptides described herein may also be modified by 2, 4-dinitrophenyl (DNP), DNP-lysine, modification by 7-Amino-4-methyl- coumarin (AMC), flourescein, NBD (7-Nitrobenz-2-Oxa-l,3-Diazole), p-nitro-anilide, rhodamine B, EDANS (5-((2-aminoethyl)amino)naphthalene-l- sulfonic acid), dabcyl, dabsyl, dansyl, texas red, FMOC, and Tamra (Tetramethylrhodamine). The GCRA peptides described herein may also be conjugated to, for example, polyethylene glycol (PEG); alkyl groups (e.g., C1-C20 straight or branched alkyl groups); fatty acid radicals; combinations of PEG, alkyl groups and fatty acid radicals (*See*, U.S. Patent 6,309,633; Soltero et al., 2001 Innovations in Pharmaceutical Technology 106-110); BSA and KLH (Keyhole Limpet Hemocyanin). The addition of PEG and other polymers which can be used to modify polypeptides of the invention is described in US20060 19347 section IX.

Also included in the invention are peptides that biologically or functional equivalent to the peptides described herein. The term "biologically equivalent" or functional equivalent" is intended to mean that the compositions of the present invention are capable of demonstrating some or all of the cGMP production modulatory effects.

GCRA peptides can also include derivatives of GCRA peptides which are intended to include hybrid and modified forms of GCRA peptides in which certain amino acids have been deleted or replaced and modifications such as where one or more amino acids have been changed to a modified amino acid or unusual amino acid and modifications such as glycosylation so long the modified form retains the biological activity of GCRA peptides. By retaining the biological activity, it is meant that cGMP and or apoptosis is induced by the GCRA peptide, although not necessarily at the same level of potency as that of a naturally-occurring GCRA peptide identified.

Preferred variants are those that have conservative amino acid substitutions made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art.

These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a GCRA polypeptide is replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a GCRA coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened to identify mutants that retain activity.

Also included within the meaning of substantially homologous is any GCRA peptide which may be isolated by virtue of cross-reactivity with antibodies to the GCRA peptide.

PREPARATION OF GCRA PEPTIDES

GCRA peptides are easily prepared using modern cloning techniques, or may be synthesized by solid state methods or by site-directed mutagenesis. A GCRA peptide may include dominant negative forms of a polypeptide.

Chemical synthesis may generally be performed using standard solution phase or solid phase peptide synthesis techniques, in which a peptide linkage occurs through the direct condensation of the amino group of one amino acid with the carboxy group of the other amino acid with the elimination of a water molecule. Peptide bond synthesis by direct condensation, as formulated above, requires suppression of the reactive character of the amino group of the first and of the carboxyl group of the second amino acid. The masking substituents must permit their ready removal, without inducing breakdown of the labile peptide molecule.

In solution phase synthesis, a wide variety of coupling methods and protecting groups may be used (*See*, Gross and Meienhofer, eds., "The Peptides: Analysis, Synthesis, Biology," Vol. 1-4 (Academic Press, 1979); Bodansky and Bodansky, "The Practice of Peptide Synthesis," 2d ed. (Springer Verlag, 1994)). In addition, intermediate purification and linear scale up are possible. Those of ordinary skill in the art will appreciate that solution synthesis requires consideration of main chain and side chain protecting groups and activation method. In addition, careful segment selection is necessary to minimize racemization during segment condensation.

Solubility considerations are also a factor. Solid phase peptide synthesis uses an insoluble polymer for support during organic synthesis. The polymer-supported peptide chain permits the use of simple washing and filtration steps instead of laborious purifications at intermediate steps. Solid-phase peptide synthesis may generally be performed according to the method of Merrifield et al., J. Am. Chem. Soc., 1963, 85:2149, which involves assembling a linear peptide chain on a resin support using protected amino acids. Solid phase peptide synthesis typically utilizes either the Boc or Fmoc strategy, which are well known in the art.

Those of ordinary skill in the art will recognize that, in solid phase synthesis, deprotection and coupling reactions must go to completion and the side-chain blocking groups must be stable throughout the synthesis. In addition, solid phase synthesis is generally most suitable when peptides are to be made on a small scale.

Acetylation of the N-terminal can be accomplished by reacting the final peptide with acetic anhydride before cleavage from the resin. C-amidation is accomplished using an appropriate resin such as methylbenzhydrylamine resin using the Boc technology.

Alternatively the GCRA peptides are produced by modern cloning techniques For example, the GCRA peptides are produced either in bacteria including, without limitation, E. coli, or in other existing systems for polypeptide or protein production (*e.g.*, Bacillus subtilis, baculovirus expression systems using Drosophila Sf9 cells, yeast or filamentous fungal expression systems, mammalian cell expression systems), or they can be chemically synthesized. If the GCRA peptide or variant peptide is to be produced in bacteria, *e.g.*, E. coli, the nucleic acid molecule encoding the polypeptide may also encode a leader sequence that permits the secretion of the mature polypeptide from the cell. Thus, the sequence encoding the polypeptide can include the pre sequence and the pro sequence of, for example, a naturally-occurring bacterial ST polypeptide. The secreted, mature polypeptide can be purified from the culture medium.

The sequence encoding a GCRA peptide described herein can be inserted into a vector capable of delivering and maintaining the nucleic acid molecule in a bacterial cell. The DNA molecule may be inserted into an autonomously replicating vector (suitable vectors include, for example, pGEM3Z and pcDNA3, and derivatives thereof). The vector nucleic acid may be a bacterial or bacteriophage DNA such as bacteriophage lambda or M13 and derivatives thereof.

Construction of a vector containing a nucleic acid described herein can be followed by transformation of a host cell such as a bacterium. Suitable bacterial hosts include but are not limited to, E. coli, B subtilis, Pseudomonas, Salmonella. The genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences.

A variety of transcriptional control sequences are well known to those in the art. The expression vector can also include a translation regulatory sequence (*e.g.*, an untranslated 5' sequence, an untranslated 3' sequence, or an internal ribosome entry site). The vector can be capable of autonomous replication or it can integrate into host DNA to ensure stability during polypeptide production.

The protein coding sequence that includes a GCRA peptide described herein can also be fused to a nucleic acid encoding a polypeptide affinity tag, *e.g.*, glutathione S-transferase (GST), maltose E binding protein, protein A, FLAG tag, hexa-histidine, myc tag or the influenza HA tag, in order to facilitate purification. The affinity tag or reporter fusion joins the reading frame of the polypeptide of interest to the reading frame of the gene encoding the affinity tag such that a translational fusion is generated. Expression of the fusion gene results in translation of a single polypeptide that includes both the polypeptide of interest and the affinity tag. In some instances where affinity tags are utilized, DNA sequence encoding a protease recognition site will be fused between the reading frames for the affinity tag and the polypeptide of interest.

Genetic constructs and methods suitable for production of immature and mature forms of the GCRA peptides and variants described herein in protein expression systems other than bacteria, and well known to those skilled in the art, can also be used to produce polypeptides in a biological system.

The peptides disclosed herein may be modified by attachment of a second molecule that confers a desired property upon the peptide, such as increased half-life in the body, for example, pegylation. Such modifications also fall within the scope of the term "variant" as used herein.

THERAPEUTIC METHODS

The present invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated that is mediated by guanylate cyclase receptor agonists. Disorders mediated by the guanylate cyclase receptor agonists include gastrointestinal disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, increasing gastrointestinal motility and obesity.Gastointestinal disorders include for example, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD)ileus (e.g., post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (e.g., constipation associated with use of medications such as opioids, osteoarthritis drugs , osteoporosis drugs; post surigical constipation, constipation associated with neuropathic disorders. Inflammatory disorders include tissue and organ inflammation such as kidney inflammation (e.g., nephritis), gastrointestinal system inflammation (e.g., Crohn's disease and ulcerative colitis); pancreatic inflammation (e.g., pancreatis), lung inflammation (e.g., bronchitis or asthma) or skin inflammation (e.g., psoriasis, eczema) . Lung Disorders include for example chronic obstructive pulmonary disease (COPD), and fibrosis. Cancer includes tissue and organ carcinogenesis including metatases such as for example gastrointestinal cancer, (e.g., gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (e.g., melanoma); oral cancer; urinary tract cancer (e.g. bladder cancer or kidney cancer); blood cancer (e.g. myeloma or leukemia) or prostate cancer. Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high tryglycerides. Liver disorders include for example cirrhosis and fibrosis. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (e.g., periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include for example benign prostatic hyperplasia (BPH). Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

The term "treatment" refers to reducing or alleviating symptoms in a subject, preventing symptoms from worsening or progressing, and/or preventing disease in a subject who is free therefrom. For a given subject, improvement in a symptom, its worsening, regression, or progression may be determined by any objective or subjective measure. Efficacy of the treatment may be measured as an improvement in morbidity or mortality (*e.g.*, lengthening of survival curve for a selected population). Thus, effective treatment would include therapy of existing disease, control of disease by slowing or stopping its progression, prevention of disease occurrence, reduction in the number or severity of symptoms, or a combination thereof. The effect may be shown in a controlled study using one or more statistically significant criteria.

Intracellular cGMP induced by exposing, *e.g.*, contacting a tissue (*e.g.*, gastrointestinals tissue) or cell with GCRA agonists. GC-C receptors are expressed throughout the GI tract starting from esophagus, duodenum, jejunum, ilium, caecum and colon. Human colon cancer cell lines (T81, CaCo-2 and HT-29) also express GC-C receptors. By inducing is meant an increase in cGMP production compared to a tissue or cell that has not been in contact with GCRA peptide or variant. Tissues or cells are directly contacted with a GCRA peptide or variant. Alternatively, the GCRA peptide or variant is administered systemically. GCRA peptide or variant are administered in an amount sufficient to increase intracellular cGMP concentration. cGMP production is measured by a cell-based assay known in the art (25).

Disorders are treated, prevented or alleviated by administering to a subject, *e.g.*, a mammal such as a human in need thereof, a therapeutically effective dose of a GCRA peptide. The GCRA peptides may be in a pharmaceutical composition in unit dose form, together with one or more pharmaceutically acceptable excipients. The term "unit dose form" refers to a single drug delivery entity, *e.g.*, a tablet, capsule, solution or inhalation formulation. The amount of peptide present should be sufficient to have a positive therapeutic effect when administered to a patient (typically, between 10 μg and 3 g). What constitutes a "positive therapeutic effect" will depend upon the particular condition being treated and will include any significant improvement in a condition readily recognized by one of skill in the art.

The GCRA peptides can be administered alone or in combination with other agents. For example the GCRA peptides can be administered in combination with inhibitors of cGMP dependent phosphodiesterase, such as, for example, suldinac sulfone, zaprinast, motapizone, vardenafil or sildenifil; one or more other chemotherapeutic agents; or anti-inflammatory drugs

such as, for example, steroids or non-steroidal anti-inflammatory drugs (NSAIDS), such as aspirin.

Combination therapy can be achieved by administering two or more agents, *e.g.*, a GCRA peptide described herein and another compound, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

The GCRA peptides described herein may be combined with phosphodiesterase inhibitors, *e.g.*, sulindae sulfone, Zaprinast, sildenafil, vardenafil or tadalafil to further enhance levels of cGMP in the target tissues or organs.

Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, *e.g.*, in the order X-Y- X, X-X-Y, Y-X-Y,Y-Y-X,X-X-Y-Y, etc.

Combination therapy can also include the administration of two or more agents via different routes or locations. For example, (a) one agent is administered orally and another agents is administered intravenously or (b) one agent is administered orally and another is administered locally. In each case, the agents can either simultaneously or sequentially. Approximated dosages for some of the combination therapy agents described herein are found in the "BNF Recommended Dose" column of tables on pages 11-17 of WO01/76632 (the data in the tables being attributed to the March 2000 British National Formulary) and can also be found

in other standard formularies and other drug prescribing directories. For some drugs, the customary presecribed dose for an indication will vary somewhat from country to country.

The GCRA peptides, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, microcrystalline cellulose (*e.g.* celphere, Celphere beads®), diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium

containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, a GCRA agonist) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. Such as mannitol, fructooligosaccharides, polyethylene glycol and other excepients. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent

such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811, incorporated fully herein by reference.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for

the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, glidants, anti-adherents, anti-static agents, surfactants (wetting agents), anti-oxidants, film- coating agents, and the like. Any such optional ingredient must be compatible with the compound described herein to insure the stability of the formulation.

The composition may contain other additives as needed, including for exanple lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffnose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and polypeptides and proteins, for example albumen.

Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents such as: BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, xanthan, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone (*e.g.*, povidone, crospovidone, copovidone, etc), methyl cellulose, Methocel, pre-gelatinized starch (e.g., STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (FMC Corporation, Marcus Hook, PA, USA), or mixtures thereof, FILLERS: talc, calcium carbonate (*e.g.*, granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, dextrose, fructose, honey, lactose anhydrate, lactose monohydrate, lactose and aspartame, lactose and cellulose, lactose and microcrystalline cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose & guar gum, molasses, sucrose,or mixtures

thereof, DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums (like gellan), low-substituted hydroxypropyl cellulose, or mixtures thereof, LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, sodium stearyl fumarate, vegetable based fatty acids lubricant, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Piano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof, ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof, ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof, and COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, gellan gum, maltodextrin, methacrylates, microcrystalline cellulose and carrageenan or mixtures thereof.

The formulation can also include other excipients and categories thereof including but not limited to L-histidine, Pluronic®, Poloxamers (such as Lutrol® and Poloxamer 188), ascorbic acid, glutathione, permeability enhancers (e.g. lipids, sodium cholate, acylcarnitine, salicylates, mixed bile salts, fatty acid micelles, chelators, fatty acid, surfactants, medium chain glycerides), protease inhibitors *(e.g.* soybean trypsin inhibitor, organic acids), pH lowering agents and absorption enhancers effective to promote bioavailability (including but not limited to those described in US6086918 and US5912014), creams and lotions (like maltodextrin and carrageenans); materials for chewable tablets (like dextrose, fructose, lactose monohydrate,

lactose and aspartame, lactose and cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose and guar gum, sorbitol crystalline); parenterals (like mannitol and povidone); plasticizers (like dibutyl sebacate, plasticizers for coatings, polyvinylacetate phthalate); powder lubricants (like glyceryl behenate); soft gelatin capsules (like sorbitol special solution); spheres for coating (like sugar spheres); spheronization agents (like glyceryl behenate and microcrystalline cellulose); suspending/gelling agents (like carrageenan, gellan gum, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, xanthan gum); sweeteners (like aspartame, aspartame and lactose, dextrose, fructose, honey, maltodextrin, maltose, mannitol, molasses, sorbitol crystalline, sorbitol special solution, sucrose); wet granulation agents (like calcium carbonate, lactose anhydrous, lactose monohydrate, maltodextrin, mannitol, microcrystalline cellulose, povidone, starch), caramel, carboxymethylcellulose sodium, cherry cream flavor and cherry flavor, citric acid anhydrous, citric acid, confectioner's sugar, D&C Red No. 33, D&C Yellow #10 Aluminum Lake, disodium edetate, ethyl alcohol 15%, FD&C Yellow No. 6 aluminum lake, FD&C Blue # 1 Aluminum Lake, FD&C Blue No. 1, FD&C blue no. 2 aluminum lake, FD&C Green No.3, FD&C Red No. 40, FD&C Yellow No. 6 Aluminum Lake, FD&C Yellow No. 6, FD&C Yellow No.10, glycerol palmitostearate, glyceryl monostearate, indigo carmine, lecithin, manitol, methyl and propyl parabens, mono ammonium glycyrrhizinate, natural and artificial orange flavor, pharmaceutical glaze, poloxamer 188, Polydextrose, polysorbate 20, polysorbate 80, polyvidone, pregelatinized corn starch, pregelatinized starch, red iron oxide, saccharin sodium, sodium carboxymethyl ether, sodium chloride, sodium citrate, sodium phosphate, strawberry flavor, synthetic black iron oxide, synthetic red iron oxide, titanium dioxide, and white wax.

Solid oral dosage forms may optionally be treated with coating systems (*e.g.* Opadry® fx film coating system, for example Opadry® blue (OY-LS-20921), Opadry® white (YS-2-7063), Opadry® white (YS- 1-7040), and black ink (S- 1-8 106).

The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycoloic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO 01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ε-caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Such formulations can be used to implants that release a polypeptide or another agent over a period of a few days, a few weeks or several months depending on the polymer, the

particle size of the polymer, and the size of the implant (*See, e.g.*, U.S. 6,620,422). Other sustained release formulations and polymers for use in are described in EP 0 467 389 A2, WO 93/24150, U.S. 5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296. U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. ,5, 980,945, WO 02/058672, WO 9726015, WO 97/04744, and US200200 19446. In such sustained release formulations microparticles (Delie and Blanco-Prieto 2005 Molecule 10:65-80) of polypeptide are combined with microparticles of polymer. One or more sustained release implants can be placed in the large intestine, the small intestine or both. U.S. 6,011,0 1 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (*i.e.* PEG 300 and PEG 400) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled releaseof the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1, U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224 materials which may include those described in WO04041195 (including the seal and enteric coating described therein) and pH-sensitive coatings that achieve delivery in the colon including those described in US4,910,021 and WO9001329. US4910021 describes using a pH-sensitive material to coat a capsule. WO9001329 describes using pH-sensitive coatings on beads containing acid, where the acid in the bead core prolongs dissolution of the pH-sensitive coating. U. S. Patent No. 5,175,003 discloses a dual mechanism polymer mixture composed of pH-sensitive enteric materials and film-forming plasticizers capable of conferring permeability to the enteric material, for use in drug-delivery systems; a matrix pellet composed of a dual mechanism polymer mixture permeated with a drug and sometimes covering a pharmaceutically neutral nucleus; a membrane- coated pellet comprising a matrix pellet coated with a dual mechanism polymer mixture envelope of the same or different composition; and a pharmaceutical dosage form containing matrix pellets. The matrix pellet releases acid-soluble drugs by diffusion in acid pH and by disintegration at pH levels of nominally about 5.0 or higher.

The GCRA peptideds described herein may be formulated in the pH triggered targeted control release systems described in WO04052339. The agents described herein may be

formulated according to the methodology described in any of WO03105812 (extruded hyrdratable polymers); WO0243767 (enzyme cleavable membrane translocators); WO03007913 and WO03086297 (mucoadhesive systems); WO02072075 (bilayer laminated formulation comprising pH lowering agent and absorption enhancer); WO04064769 (amidated polypeptides); WO05063156 (solid lipid suspension with pseudotropic and/or thixotropic properties upon melting); WO03035029 and WO03035041 (erodible, gastric retentive dosage forms); US5007790 and US5972389 (sustained release dosage forms); WO041 1271 1 (oral extended release compositions); WO05027878, WO02072033, and WO02072034 (delayed release compositions with natural or synthetic gum); WO05030182 (controlled release formulations with an ascending rate of release); WO05048998 (microencapsulation system); US Patent 5,952,314 (biopolymer); US5,108,758 (glassy amylose matrix delivery); US 5,840,860 (modified starch based delivery). JP10324642 (delivery system comprising chitosan and gastric resistant material such as wheat gliadin or zein); US5,866,619 and US6,368,629 (saccharide containing polymer); US 6,531,152 (describes a drug delivery system containing a water soluble core (Ca pectinate or other water-insoluble polymers) and outer coat which bursts (*e.g.* hydrophobic polymer-Eudragrit)); US 6,234,464; US 6,403,130 (coating with polymer containing casein and high methoxy pectin; WO0174 175 (Maillard reaction product); WO05063206 (solubility increasing formulation); WO040 19872 (transferring fusion proteins).

The GCRA peptides described herein may be formulated using gastrointestinal retention system technology (GIRES; Merrion Pharmaceuticals). GIRES comprises a controlled-release dosage form inside an inflatable pouch, which is placed in a drug capsule for oral administration. Upon dissolution of the capsule, a gas-generating system inflates the pouch in the stomach where it is retained for 16-24 hours, all the time releasing agents described herein.

The GCRA peptides described herein can be formulated in an osmotic device including the ones disclosed in US4,503,030, US5,609,590 and US5,358,502. US4,503,030 discloses an osmotic device for dispensing a drug to certain pH regions of the gastrointestinal tract. More particularly, the invention relates to an osmotic device comprising a wall formed of a semi-permeable pH sensitive composition that surrounds a compartment containing a drug, with a passageway through the wall connecting the exterior of the device with the compartment. The device delivers the drug at a controlled rate in the region of the gastrointestinal tract having a pH of less than 3.5, and the device self- destructs and releases all its drug in the region of the

gastrointestinal tract having a pH greater than 3.5, thereby providing total availability for drug absorption. U.S. Patent Nos. 5,609,590 and 5, 358,502 disclose an osmotic bursting device for dispensing a beneficial agent to an aqueous environment. The device comprises a beneficial agent and osmagent surrounded at least in part by a semi-permeable membrane. The beneficial agent may also function as the osmagent. The semi-permeable membrane is permeable to water and substantially impermeable to the beneficial agent and osmagent. A trigger means is attached to the semi-permeable membrane *(e.g.*,joins two capsule halves). The trigger means is activated by a pH of from 3 to 9 and triggers the eventual, but sudden, delivery of the beneficial agent. These devices enable the pH-triggered release of the beneficial agent core as a bolus by osmotic bursting.

EXEMPLARY AGENTS FOR COMBINATION THERAPY

Analgesic Agents

The GCRA peptides described herein can be used in combination therapy with an analgesic agent, e.g., an analgesic compound or an analgesic polypeptide. These polypeptides and compounds can be administered with the GCRA peptides described herein (simultaneously or sequentially). They can also be optionally covalently linked or attached to an agent described herein to create therapeutic conjugates. Among the useful analgesic agents are: Ca channel blockers, 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HTl receptor antagonists), opioid receptor agonists (loperamide, fedotozine, and fentanyl), NKl receptor antagonists, CCK receptor agonists (*e.g.*, loxiglumide), NKl receptor antagonists, NK3 receptor antagonists, norepinephrine-serotonin reuptake inhibitors (NSRI), vanilloid and cannabanoid receptor agonists, and sialorphin. Analgesics agents in the various classes are described in the literature.

Among the useful analgesic polypeptides are sialorphin-related polypeptides, including those comprising the amino acid sequence QHNPR (SEQ ID NO:), including: VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:). Sialorphin-related polypeptides bind to neprilysin and inhibit neprilysin- mediated breakdown of substance P and Met-enkephalin. Thus, compounds or polypeptides that are inhibitors of neprilysin are useful analgesic agents which can be administered with the polypeptides described herein in a co-therapy or linked to the polypeptides described herein, *e.g.*,

by a covalent bond. Sialophin and related polypeptides are described in U.S. Patent 6,589,750; U.S. 20030078200 Al; and WO 02/051435 A2.

Opioid receptor antagonists and agonists can be administered with the GCRA peptides described herein in co-therapy or linked to the agent described herein, *e.g.*, by a covalent bond. For example, opioid receptor antagonists such as naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine are thought to be useful in the treatment of IBS. It can be useful to formulate opioid antagonists of this type is a delayed and sustained release formulation such that initial release of the antagonist is in the mid to distal small intestine and/or ascending colon. Such antagonists are described in WO 01/32180 A2. Enkephalin pentapeptide (HOE825; Tyr-D-Lys-Gly-Phe-L-homoserine) is an agonist of the mu and delta opioid receptors and is thought to be useful for increasing intestinal motility {Eur. J. Pharm. 219:445, 1992), and this polypeptide can be used in conjunction with the polypeptides described herein. Also useful is trimebutine which is thought to bind to mu/delta/kappa opioid receptors and activate release of motilin and modulate the release of gastrin, vasoactive intestinal polypeptide, gastrin and glucagons. Kappa opioid receptor agonists such as fedotozine, asimadoline, and ketocyclazocine, and compounds described in WO03/097051 and WO05/007626 can be used with or linked to the polypeptides described herein. In addition, mu opioid receptor agonists such as morphine, diphenyloxylate, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH 2; WO 01/019849 Al) and loperamide can be used.

Tyr-Arg (kyotorphin) is a dipeptide that acts by stimulating the release of met-enkephalins to elicit an analgesic effect (J. Biol. Chem 262:8165, 1987). Kyotorphin can be used with or linked to the GCRA peptides described herein.

Chromogranin-derived polypeptide (CgA 47-66; *See, e.g.*, Ghia et al. 2004 Regulatory polypeptides 119:199) can be used with or linked to the GCRA peptides described herein.

CCK receptor agonists such as caerulein from amphibians and other species are useful analgesic agents that can be used with or linked to the GCRA peptides described herein.

Conotoxin polypeptides represent a large class of analgesic polypeptides that act at voltage gated calcium channels, NMDA receptors or nicotinic receptors. These polypeptides can be used with or linked to the polypeptides described herein.

Peptide analogs of thymulin (FR Application 2830451) can have analgesic activity and can be used with or linked to the polypeptides described herein.

CCK (CCKa or CCKb) receptor antagonists, including loxiglumide and dexloxiglumide (the R- isomer of loxiglumide) (WO 88/05774) can have analgesic activity and can be used with or linked to the polypeptides described herein.

Other useful analgesic agents include 5-HT4 agonists such as tegaserod (Zelnorm®), mosapride, metoclopramide, zacopride, cisapride, renzapride, benzimidazolone derivatives such as BIMU 1 and BIMU 8, and lirexapride. Such agonists are described in: EP1321 142 Al, WO 03/053432A1, EP 505322 Al, EP 505322 Bl, US 5,510,353, EP 507672 Al, EP 507672 Bl, and US 5,273,983.

Calcium channel blockers such as ziconotide and related compounds described in, for example, EP625162B1, US 5,364,842, US 5,587,454, US 5,824,645, US 5,859,186, US 5,994,305, US 6087,091, US 6,136,786, WO 93/13128 Al, EP 1336409 Al, EP 835126 Al, EP 835126 Bl, US 5,795,864, US 5,891,849, US 6,054,429, WO 97/01351 Al, can be used with or linked to the polypeptides described herein.

Various antagonists of the NK-I, NK-2, and NK-3 receptors (for a review see Giardina et al. 2003.Drugs 6:758) can be can be used with or linked to the polypeptides described herein.

NKl receptor antagonists such as: aprepitant (Merck & Co Inc), vofopitant, ezlopitant (Pfizer, Inc.), R-673 (Hoffmann-La Roche Ltd), SR-48968 (Sanofi Synthelabo), CP-122,721 (Pfizer, Inc.), GW679769 (Glaxo Smith Kline), TAK-637 (Takeda/Abbot), SR-14033, and related compounds described in, for example, EP 873753 Al, US 20010006972 Al, US 20030109417 Al, WO 01/52844 Al, can be used with or linked to the polypeptides described herein.

NK-2 receptor antagonists such as nepadutant (Menarini Ricerche SpA), saredutant (Sanofi- Synthelabo), GW597599 (Glaxo Smith Kline), SR-144190 (Sanofi-Synthelabo) and UK-290795 (Pfizer Inc) can be used with or linked to the polypeptides described herein.

NK3 receptor antagonists such as osanetant (SR-142801; Sanofi-Synthelabo), SSR-241586, talnetant and related compounds described in, for example, WO 02/094187 A2, EP 876347 Al, WO 97/21680 Al, US 6,277,862, WO 98/1 1090, WO 95/28418, WO 97/19927, and Boden et al. (J Med Chem. 39:1664-75, 1996) can be used with or linked to the polypeptides described herein.

Norepinephrine-serotonin reuptake inhibitors (NSRI) such as milnacipran and related compounds described in WO 03/077897 Al can be used with or linked to the polypeptides described herein.

Vanilloid receptor antagonists such as arvanil and related compouds described in WO 01/64212 Al can be used with or linked to the polypeptides described herein.

The analgesic polypeptides and compounds can be administered with the polypeptides and agonists described herein (simultaneously or sequentially). The analgesic agents can also be covalently linked to the polypeptides and agonists described herein to create therapeutic conjugates. Where the analgesic is a polypeptide and is covalently linked to an agent described herein the resulting polypeptide may also include at least one trypsin cleavage site. When present within the polypeptide, the analgesic polypeptide may be preceded by (if it is at the carboxy terminus) or followed by (if it is at the amino terminus) a trypsin cleavage site that allows release of the analgesic polypeptide.

In addition to sialorphin-related polypeptides, analgesic polypeptides include: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, ziconotide, and substance P.

Agents to Treat Gastrointestinal Disorders

Examples of additional therapeutic agents to treat gastrointestinal and other disorders include agents to treat constipation (*e.g.*, a chloride channel activator such as the bicylic fatty acid, Lubiprostone (formerly known as SPI-0211; Sucampo Pharmaceuticals, Inc.; Bethesda, MD), a laxative (*e.g.* a bulk-forming laxative (e.g. nonstarch polysaccharides, Colonel Tablet (polycarbophil calcium), Plantago Ovata®, Equalactin® (Calcium Polycarbophil)), fiber (*e.g.* FIBERCON® (Calcium Polycarbophil), an osmotic laxative, a stimulant laxative (such as diphenylmethanes (*e.g.* bisacodyl), anthraquinones (*e.g.* cascara, senna), and surfactant laxatives (*e.g.* castor oil, docusates), an emollient/lubricating agent (such as mineral oil, glycerine, and docusates), MiraLax (Braintree Laboratories, Braintree MA), dexloxiglumide (Forest Laboratories, also known as CR 2017 Rottapharm (Rotta Research Laboratorium SpA)), saline laxatives, enemas, suppositories, and CR 3700 (Rottapharm (Rotta Research Laboratorium SpA); acid reducing agents such as proton pump inhibitors (*e.g.*, omeprazole (Prilosec®), esomeprazole (Nexium®), lansoprazole (Prevacid®), pantoprazole (Protonix®) and rabeprazole (Aciphex®)) and Histamine H2 -receptor antagonist (also known as H2 receptor blockers including

cimetidine, ranitidine, famotidine and nizatidine); prokinetic agents including itopride, octreotide, bethanechol, metoclopramide (Reglan®), domperidone (Motilium®), erythromycin (and derivatives thereof) or cisapride (propulsid®); Prokineticin polypeptides homologs, variants and chimeras thereof including those described in US 7,052,674 which can be used with or linked to the polypeptides described herein; pro-motility agents such as the vasostatin-derived polypeptide, chromogranin A (4-16) (*See, e.g.*, Ghia et al. 2004 Regulatory polypeptides 121:31) or motilin agonists (*e.g.*, GM-611 or mitemcinal fumarate) or nociceptin/Orphanin FQ receptor modulators (US20050169917); other peptides which can bind to and/or activate GC-C including those described in US20050287067; complete or partial 5HT (*e.g.* 5HTl, 5HT2, 5HT3, 5HT4) receptor agonists or antagonists (including 5HT1A antagonists (*e.g.* AGI-OOl (AGI therapeutics), 5HT2B antagonists (*e.g.* PGN 1091 and PGNl 164 (Pharmagene Laboratories Limited), and 5HT4 receptor agonists (such as tegaserod (ZELNORM®), prucalopride, mosapride, metoclopramide, zacopride, cisapride, renzapride, benzimidazolone derivatives such as BIMU 1 and BIMU 8, and lirexapride). Such agonists/modulators are described in: EP1321142 Al, WO 03/053432A1, EP 505322 Al, EP 505322 Bl, US 5,510,353, EP 507672 Al, EP 507672 Bl, US 5,273,983, and US 6,951,867); 5HT3 receptor agonists such as MKC-733; and 5HT3 receptor antagonists such as DDP-225 (MCI-225; Dynogen Pharmaceuticals, Inc.), cilansetron (Calmactin®), alosetron (Lotronex®), Ondansetron HCl (Zofran®), Dolasetron (ANZEMET®), palonosetron (Aloxi®), Granisetron (Kytril®), YM060(ramosetron; Astellas Pharma Inc.; ramosetron may be given as a daily dose of 0.002 to 0.02 mg as described in EP01588707) and ATI-7000 (Aryx Therapeutics, Santa Clara CA); muscarinic receptor agonists; anti-inflammatory agents; antispasmodics including but not limited to anticholinergic drugs (like dicyclomine (*e.g.* Colimex®, Formulex®, Lomine®, Protylol®, Visceral®, Spasmoban®, Bentyl®, Bentylol®), hyoscyamine (*e.g.* IB-Stat®, Nulev®, Levsin®, Levbid®, Levsinex Timecaps®, Levsin/SL®, Anaspaz®, A-Spas S/L®, Cystospaz®, Cystospaz-M®, Donnamar®, Colidrops Liquid Pediatric®, Gastrosed®, Hyco Elixir®, Hyosol®, Hyospaz®, Hyosyne®, Losamine®, Medispaz®, Neosol®, Spacol®, Spasdel®, Symax®, Symax SL®), Donnatal (*e.g.* Donnatal Extentabs®), clidinium (e.g. Quarzan, in combination with Librium = Librax), methantheline (*e.g.* Banthine), Mepenzolate (*e.g.* Cantil), homatropine (*e.g.* hycodan, Homapin), Propantheline bromide (*e.g.* Pro-Banthine), Glycopyrrolate (*e.g.* Robinul®, Robinul Forte®), scopolamine (*e.g.* Transderm-Scop®, Transderm-V®), hyosine-N-butylbromide (*e.g.*

Buscopan®), Pirenzepine (*e.g.* Gastrozepin®) Propantheline Bromide (*e.g.* Propanthel®), dicycloverine (*e.g.* Merbentyl®), glycopyrronium bromide (*e.g.* Glycopyrrolate®), hyoscine hydrobromide, hyoscine methobromide, methanthelinium, and octatropine); peppermint oil; and direct smooth muscle relaxants like cimetropium bromide, mebeverine (DUSPATAL®, DUSPATALIN®, COLOFAC MR®, COLOTAL®), otilonium bromide (octilonium), pinaverium (e.g. Dicetel® (pinaverium bromide; Solvay S. A.)), Spasfon® (hydrated phloroglucinol and trimethylphloroglucinol)and trimebutine (including trimebutine maleate (Modulon®); antidepressants, including but not limited to those listed herein, as well as tricyclic antidepressants like amitriptyline (Elavil®), desipramine (Norpramin®), imipramine (Tofranil®), amoxapine (Asendin®), nortriptyline; the selective serotonin reuptake inhibitors (SSRTs) like paroxetine (Paxil®), fluoxetine (Prozac®), sertraline (Zoloft®), and citralopram (Celexa®); and others like doxepin (Sinequan®) and trazodone (Desyrel®); centrally-acting analgesic agents such as opioid receptor agonists, opioid receptor antagonists (e.g., naltrexone); agents for the treatment of Inflammatory bowel disease; agents for the treatment of Crohn's disease and/or ulcerative colitis (*e.g.*, alequel (Enzo Biochem, Inc.; Farmingsale, NY), the anti-inflammatory polypeptide RDP58 (Genzyme, Inc.; Cambridge, MA), and TRAFICET-EN™ (ChemoCentryx, Inc.; San Carlos, CA); agents that treat gastrointestinal or visceral pain; agents that increase cGMP levels (as described in US20040121994) like adrenergic receptor antagonists, dopamine receptor agonists and PDE (phosphodiesterase) inhibitors including but not limited to those disclosed herein; purgatives that draw fluids to the intestine (*e.g.*, VISICOL®, a combination of sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrate); Corticotropin Releasing Factor (CRF) receptor antagonists (including NBI-34041 (Neurocrine Biosciences, San Diego, CA), CRH9-41, astressin, R121919 (Janssen Pharmaceutica), CP154,526, NBI-27914, Antalarmin, DMP696 (Bristol-Myers Squibb) CP-316,311 (Pfizer, Inc.), SB723620 (GSK), GW876008 (Neurocrine/Glaxo Smith Kline), ONO-2333Ms (Ono Pharmaceuticals), TS-041 (Janssen), AAG561 (Novartis) and those disclosed in US 5,063,245, US 5,861,398, US20040224964, US20040198726, US20040176400, US20040171607, US20040110815, US20040006066, and US20050209253); glucagon- like polypeptides (glp-1) and analogues thereof (including exendin-4 and GTP-010 (Gastrotech Pharma A)) and inhibitors of DPP-IV (DPP-IV mediates the inactivation of glp-1); tofisopam, enantiomerically-pure R-tofisopam, and pharmaceutically-acceptable salts thereof (US

20040229867); tricyclic anti-depressants of the dibenzothiazepine type including but not limited to Dextofisopam® (Vela Pharmaceuticals), tianeptine (Stablon®) and other agents described in US 6,683,072; (E)-4 (1 ,3bis(cyclohexylmethyl)-l ,2,34,-tetrahydro-2,6-diono-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester and related compounds described in WO 02/067942; the probiotic PROBACTRIX® (The BioBalance Corporation; New York, NY) which contains microorganisms useful in the treatment of gastrointestinal disorders; antidiarrheal drugs including but not limited to loperamide (Imodium, Pepto Diarrhea), diphenoxylate with atropine (Lomotil, Lomocot), cholestyramine (Questran, Cholybar), atropine (Co-Phenotrope, Diarsed, Diphenoxylate, Lofene, Logen, Lonox, Vi-Atro, atropine sulfate injection) and Xifaxan® (rifaximin; Salix Pharmaceuticals Ltd), TZP-201(Tranzyme Pharma Inc.), the neuronal acetylcholine receptor (nAChR) blocker AGI-004 (AGI therapeutics), and bismuth subsalicylate (Pepto-bismol); anxiolytic drugs including but not limited toAtivan (lorazepam), alprazolam (Xanax®), chlordiazepoxide/clidinium (Librium®, Librax®), clonazepam (Klonopin®), clorazepate (Tranxene®), diazepam (Valium®), estazolam (ProSom®), flurazepam (Dalmane®), oxazepam (Serax®), prazepam (Centrax®), temazepam (Restoril®), triazolam (Halcion®; Bedelix® (Montmorillonite beidellitic; Ipsen Ltd), Solvay SLV332 (ArQule Inc), YKP (SK Pharma), Asimadoline (Tioga Pharmaceuticals/Merck), AGI-003 (AGI Therapeutics); neurokinin antagonists including those described in US20060040950; potassium channel modulators including those described in US7,002,015; the serotonin modulator AZD7371 (AstraZeneca Plc); M3 muscarinic receptor antagonists such as darifenacin (Enablex; Novartis AG and zamifenacin (Pfizer); herbal and natural therapies including but not limited to acidophilus, chamomile tea, evening primrose oil, fennel seeds,wormwood, comfrey, and compounds of Bao-Ji-Wan (magnolol, honokiol, imperatorin, and isoimperatorin) as in US6923992; and compositions comprising lysine and an anti-stress agent for the treatment of irritable bowel syndrome as described in EPO 1550443.

Insulin and Insulin Modulating Agents

The GCRA peptides described herein can be used in combination therapy with insulin and related compounds including primate, rodent, or rabbit insulin including biologically active variants thereof including allelic variants, more preferably human insulin available in recombinant form. Sources of human insulin include pharmaceutically acceptable and sterile

formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin™ (human insulin rDNA origin). *See*, the THE PHYSICIAN'S DESK REFERENCE, 55.sup.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins).

The GCRA peptides described herein can also be used in combination therapy with agents that can boost insulin effects or levels of a subject upon administration, *e.g.* glipizide and/or rosiglitazone. The polypeptides and agonistsdescribed herein can be used in combitherapy with SYMLIN® (pramlintide acetate) and Exenatide® (synthetic exendin-4; a 39 aa polypeptide).

Agents for the Treatment of Postoperative Ileus

The GCRA peptides described herein can also be used in combination therapy with agents (*e.g.*, Entereg™ (alvimopan; formerly called ado lor/ ADL 8-2698), conivaptan and related agents describe in US 6,645,959) used for the treatment of postoperative ileus and other disorders.

Anti-Hypertensive Agents

The GCRA peptides described herein can be used in combination therapy with an anti-hypertensive agent including but not limited to: (1) diuretics, such as thiazides, including chlorthalidone, chlorthiazide, dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, and hydrochlorothiazide; loop diuretics, such as bumetanide, ethacrynic acid, furosemide, and torsemide; potassium sparing agents, such as amiloride, and triamterene; carbonic anhydrase inhibitors, osmotics(such as glycerin) and aldosterone antagonists, such as spironolactone, epirenone, and the like; (2) beta-adrenergic blockers such as acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol, and timolol, and the like; (3) calcium channel blockers such as amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, diltiazem, efonidipine, felodipine, gallopamil, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodepine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil, and the like; (4) angiotensin converting enzyme (ACE) inhibitors such as benazepril; captopril; ceranapril; cilazapril; delapril; enalapril; enalopril; fosinopril; imidapril; lisinopril; losinopril; moexipril;

quinapril; quinaprilat; ramipril; perindopril; perindropril; quanipril; spirapril; tenocapril; trandolapril, and zofenopril, and the like; (5) neutral endopeptidase inhibitors such as omapatrilat, cadoxatril and ecadotril, fosidotril, sampatrilat, AVE7688, ER4030, and the like; (6) endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; (7) vasodilators such as hydralazine, clonidine, minoxidil, and nicotinyl alcohol, and the like; (8) angiotensin II receptor antagonists such as aprosartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, pratosartan, tasosartan, telmisartan, valsartan, and EXP-3137, FI6828K, and RNH6270, and the like; (9) α/β adrenergic blockers such as nipradilol, arotinolol and amosulalol, and the like; (10) alpha 1 blockers, such as terazosin, urapidil, prazosin, tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, and XENOlO, and the like; (11) alpha 2 agonists such as lofexidine, tiamenidine, moxonidine, rilmenidine and guanobenz, and the like; (12) aldosterone inhibitors, and the like; and (13) angiopoietin-2 -binding agents such as those disclosed in WO03/030833. Specific anti-hypertensive agents that can be used in combination with polypeptides and agonists described herein include, but are not limited to: diuretics, such as thiazides (*e.g.*, chlorthalidone, cyclothiazide (CAS RN 2259-96-3), chlorothiazide (CAS RN 72956-09-3, which may be prepared as disclosed in US2809194), dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, bendroflumethazide, methyclothazide, polythiazide, trichlormethazide, chlorthalidone, indapamide, metolazone, quinethazone, althiazide (CAS RN 5588-16-9, which may be prepared as disclosed in British Patent No. 902,658), benzthiazide (CAS RN 91-33-8, which may be prepared as disclosed in US3108097), buthiazide (which may be prepared as disclosed in British Patent Nos. 861 ,367), and hydrochlorothiazide), loop diuretics (*e.g.* bumetanide, ethacrynic acid, furosemide, and torasemide), potassium sparing agents (*e.g.* amiloride, and triamterene (CAS Number 396-01-O)), and aldosterone antagonists (*e.g.* spironolactone (CAS Number 52-01-7), epirenone, and the like); β-adrenergic blockers such as Arniodarone (Cordarone, Pacerone), bunolol hydrochloride (CAS RN 31969-05-8, Parke-Davis), acebutolol (±N-[3-Acetyl-4-[2-hydroxy-3-[(1 methylethyl)amino]propoxy]phenyl]-butanamide, or (±)-3'-Acetyl-4'-[2-hydroxy -3-(isopropylamino) propoxy] butyranilide), acebutolol hydrochloride (*e.g.* Sectral®, Wyeth-Ayerst), alprenolol hydrochloride (CAS RN 13707-88-5 see Netherlands Patent Application No. 6,605,692), atenolol (*e.g.* Tenormin®, AstraZeneca), carteolol hydrochloride (*e.g.* Cartrol® Filmtab®, Abbott), Celiprolol hydrochloride (CAS RN 57470-78-7, also see in US4034009),

cetamolol hydrochloride (CAS RN 77590-95-5, see also US4059622), labetalol hydrochloride (e.g. Normodyne®, Schering), esmolol hydrochloride (e.g. Brevibloc®, Baxter), levobetaxolol hydrochloride (e.g. Betaxon™ Ophthalmic Suspension, Alcon), levobunolol hydrochloride (e.g. Betagan® Liquifilm® with C CAP® Compliance Cap, Allergan), nadolol (e.g. Nadolol, Mylan), practolol (CAS RN 6673-35-4, see also US3408387), propranolol hydrochloride (CAS RN 318-98-9), sotalol hydrochloride (e.g. Betapace AF™,Berlex), timolol (2-Propanol,l-[(l,l-dimethylethyl)amino]-3-[[4-4(4-morpholinyl)-l,2,5-thiadiazol-3-yl]oxy]-, hemihydrate, (S)-, CAS RN 91524-16-2), timolol maleate (S)-l -[(1,1 -dimethylethyl) amino]-3-[[4- (4-morpholinyl)-l,2,5-thiadiazol -3- yl] oxy]-2-propanol (Z)-2-butenedioate (1 :1) salt, CAS RN 26921-17-5), bisoprolol (2-Propanol, l-[4-[[2-(l-methylethoxy)ethoxy]-methyl]phenoxyl]-3-[(l-meth- ylethyl)amino]-, (±), CAS RN 66722-44-9), bisoprolol fumarate (such as (±)-l-[4-[[2-(l-Methylethoxy) ethoxy]methyl]phenoxy]-3-[(l-methylethyl)amino]-2-propanol (E) -2-butenedioate (2:1) (salt), *e.g.*, Zebeta™ , Lederle Consumer), nebivalol (2H-l-Benzopyran-2-methanol, αα'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-, CAS RN 99200-09-6 see also U.S. Pat. No. 4,654,362), cicloprolol hydrochloride, such 2-Propanol, l-[4-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-[l-methylethyl)amino]-, hydrochloride, A.A.S. RN 63686-79-3), dexpropranolol hydrochloride (2-Propanol,l-[l-methylethy)-amino]-3-(l-naphthalenyloxy)-hydrochloride (CAS RN 13071-11-9), diacetolol hydrochloride (Acetamide, N-[3-acetyl-4-[2-hydroxy-3-[(l-methyl-ethyl)amino]propoxy] [phenyl]-, monohydrochloride CAS RN 69796-04-9), dilevalol hydrochloride (Benzamide, 2-hydroxy-5-[l-hydroxy-2-[l-methyl-3-phenylpropyl)amino]ethyl]-, monohydrochloride, CAS RN 75659-08-4), exaprolol hydrochloride (2-Propanol, 1 -(2-cyclohexylphenoxy)-3 - [(1 -methylethyl)amino] -, hydrochloride CAS RN 59333-90-3), flestolol sulfate (Benzoic acid, 2-fluro-,3-[[2-[aminocarbonyl)amino]- - dimethylethyl]amino]-2-hydroxypropyl ester, (+)- sulfate (1 :1) (salt), CAS RN 88844-73-9; metalol hydrochloride (Methanesulfonamide, N-[4-[l-hydroxy-2-(methylamino)propyl]phenyl]-, monohydrochloride CAS RN 7701-65-7), metoprolol 2-Propanol, l-[4-(2- methoxyethyl)phenoxy]-3-[l-methylethyl)amino]-; CAS RN 37350-58-6), metoprolol tartrate (such as 2-Propanol, l-[4-(2-methoxyethyl)phenoxy]-3-[(l-methylethyl)amino]-, *e.g.*, Lopressor®, Novartis), pamatolol sulfate (Carbamic acid, [2-[4-[2-hydroxy-3-[(l- methylethyl)amino]propoxyl]phenyl]-ethyl]-, methyl ester, (±) sulfate (salt) (2:1), CAS RN 59954-01-7), penbutolol sulfate (2-Propanol, l-(2-cyclopentylphenoxy)-3-[l,l-

dimethyle- thyl)amino] 1 , (S)-, sulfate (2:1) (salt), CAS RN 38363-32-5), practolol (Acetamide, N-[4-[2- hydroxy-3-[(1-methylethyl)amino]-propoxy]phenyl]-, CAS RN 6673-35-4;) tiprenolol hydrochloride (Propanol, 1-[(1-methylethyl)amino]-3-[2-(methylthio)-phenoxy]-, hydrochloride, (±), CAS RN 39832-43-4), tolamolol (Benzamide, 4-[2-[[2-hydroxy-3-(2-methylphenoxy)-propyl] amino] ethoxy[]-, CAS RN 38103-61-6), bopindolol, indenolol, pindolol, propanolol, tertatolol, and tilisolol, and the like; calcium channel blockers such as besylate salt of amlodipine (such as 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1 ,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate, e.g., Norvasc®, Pfizer), clentiazem maleate (1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-(2S-cis)-, (Z)-2-butenedioate (1 :1), see also US4567195), isradipine (3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester, (±)-4(4-benzofurazanyl)- 1 ,4-dihydro-2,6-dimethyl-3 ,5 - pyridinedicarboxylate, see also US4466972); nimodipine (such as is isopropyl (2- methoxyethyl) 1, 4- dihydro -2,6- dimethyl -4- (3-nitrophenyl) -3,5- pyridine - dicarboxylate, *e.g.* Nimotop®, Bayer), felodipine (such as ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate- , *e.g.* Plendil® Extended-Release, AstraZeneca LP), nilvadipine (3,5-Pyridinedicarboxylic acid, 2-cyano-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-,3-methyl 5-(1-methylethyl) ester, also see US3799934), nifedipine (such as 3, 5 -pyridinedicarboxylic acid,1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, *e.g.*, Procardia XL® Extended Release Tablets, Pfizer), diltiazem hydrochloride (such as 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis., *e.g.*, Tiazac®, Forest), verapamil hydrochloride (such as benzeneacetronitrile, (alpha)-[[3-[[2-(3,4-dimethoxyphenyl) ethyl]methylamino]propyl] -3 ,4-dimethoxy-(alpha)-(1 -methylethyl) hydrochloride, *e.g.*, Isoptin® SR, Knoll Labs), teludipine hydrochloride (3,5-Pyridinedicarboxylic acid, 2-[(dimethylamino)methyl]4-[2-[(lE)-3-(1,1-dimethylethoxy)-3-oxo- 1-propenyl]phenyl]-1,4-dihydro-6-methyl-, diethyl ester, monohydrochloride) CAS RN 108700-03-4), belfosdil (Phosphonic acid, [2-(2-phenoxy ethyl)- 1,3 -propane- diyl]bis-, tetrabutyl ester CAS RN 103486-79-9), fostedil (Phosphonic acid, [[4-(2-benzothiazolyl)phenyl]methyl]-, diethyl ester CAS RN 75889-62-2), aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, efonidipine, gallopamil, lacidipine, lemildipine, lercanidipine, monatepil maleate (1-Piperazinebutanamide, N-(6, 11 -dihydrodibenzo(b,e)thiepin- 11 -yl)$_4$-(4-

fluorophenyl)-, (+)-, (Z)-2-butenedioate (1 :1) (±)-N-(6,l l-Dihydrodibenzo(b,e)thiep- in-l l-yl)-4-(p- fluorophenyl)-l-piperazinebutyramide maleate (1 :1) CAS RN 132046-06-1), nicardipine, nisoldipine, nitrendipine, manidipine, pranidipine, and the like; T-channel calcium antagonists such as mibefradil; angiotensin converting enzyme (ACE) inhibitors such as benazepril, benazepril hydrochloride (such as 3-[[l-(ethoxycarbonyl)-3- phenyl-(1 S)-propyl]amino]-2,3 ,4,5-tetrahydro-2-oxo- 1 H - 1 -(3 S)-benzazepine- 1 -acetic acid monohydrochloride, *e.g.*, Lotrel®, Novartis), captopril (such as l-[(2S)-3-mercapto-2- methylpropionyl]-L-proline, *e.g.*, Captopril, Mylan, CAS RN 62571-86-2 and others disclosed in US4046889), ceranapril (and others disclosed in US4452790), cetapril (alacepril, Dainippon disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986)), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987), indalapril (delapril hydrochloride (2H-1,2,4- Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1- dioxide CAS RN 2259-96-3); disclosed in US4385051), enalapril (and others disclosed in US4374829), enalopril, enaloprilat, fosinopril, ((such as L-proline, 4-cyclohexyl-l-[[[2-methyl- l-(l-oxopropoxy) propoxy](4-phenylbutyl) phosphinyl]acetyl]-, sodium salt, *e.g.*, Monopril, Bristol-Myers Squibb and others disclosed in US4168267), fosinopril sodium (L- Proline, 4-cyclohexyl-l-[[(R)-[(lS)-2-methyl-l-(l-ox- opropoxy)propox), imidapril, indolapril (Schering, disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983)), lisinopril (Merck), losinopril, moexipril, moexipril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(lS)- 1 -(ethoxycarbonyl)-3-phenylpropyl]amino]- 1 -oxopropyl]- 1 ,- 2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, (3S)- CAS RN 82586-52-5), quinapril, quinaprilat, ramipril (Hoechsst) disclosed in EP 79022 and Curr. Ther. Res. 40:74 (1986), perindopril erbumine (such as 2S,3aS,7aS- 1 -[(S)-N-[(S)- 1 -Carboxybutyljalanyljhexahydro^-indolinecarboxylic acid, 1 -ethyl ester, compound with tert-butylamine (1 :1), *e.g.*, Aceon®, Solvay), perindopril (Servier, disclosed in Eur. J. clin. Pharmacol. 31 :519 (1987)), quanipril (disclosed in US4344949), spirapril (Schering, disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5): 173 (1986)), tenocapril, trandolapril, zofenopril (and others disclosed in US4316906), rentiapril (fentiapril, disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983)), pivopril, YS980, teprotide (Bradykinin potentiator BPP9a CAS RN 35115-60-7), BRL 36,378 (Smith Kline Beecham, see EP80822 and EP60668), MC-838 (Chugai, see CA. 102:72588v and Jap. J. Pharmacol. 40:373 (1986), CGS 14824 (Ciba-Geigy, 3-([l-ethoxycarbonyl-3-phenyl-(lS)-propyl]amino)-2,3,4,5-tetrahydro-2-ox- o-l-(3S)-benzazepine-l

acetic acid HCl, see U.K. Patent No. 2103614), CGS 16,617 (Ciba- Geigy, 3(S)-[[(lS)-5-amino-l-carboxypentyl]amino]-2,3,4,- 5-tetrahydro-2-oxo-lH-l- benzazepine-1-ethanoic acid, see US4473575), Ru 44570 (Hoechst, see Arzneimittelforschung 34:1254 (1985)), R 31-2201 (Hoffman-LaRoche see FEBS Lett. 165:201 (1984)), CI925 (Pharmacologist 26:243, 266 (1984)), WY-44221 (Wyeth, see J. Med. Chem. 26:394 (1983)), and those disclosed in US2003006922 (paragraph 28), US4337201, US4432971 (phosphonamidates); neutral endopeptidase inhibitors such as omapatrilat (Vanlev®), CGS 30440, cadoxatril and ecadotril, fasidotril (also known as aladotril or alatriopril), sampatrilat, mixanpril, and gemopatrilat, AVE7688, ER4030, and those disclosed in US5362727, US5366973, US5225401, US4722810, US5223516, US4749688, US5552397, US5504080, US5612359, US5525723, EP0599444, EP0481522, EP0599444, EP0595610, EP0534363, EP534396, EP534492, EP0629627; endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; vasodilators such as hydralazine (apresoline), clonidine (clonidine hydrochloride (1H-Imidazol- 2-amine, N-(2,6-dichlorophenyl)4,5-dihydro-, monohydrochloride CAS RN 4205-91-8), catapres, minoxidil (loniten), nicotinyl alcohol (roniacol), diltiazem hydrochloride (such as 1,5- Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4- methoxyphenyl)-, monohydrochloride, (+)-cis, e.g., Tiazac®, Forest), isosorbide dinitrate (such as l,4:3,6-dianhydro-D-glucitol 2,5-dinitrate *e.g.*, Isordil® Titradose®, Wyeth- Ayerst), sosorbide mononitrate (such as l,4:3,6-dianhydro-D-glucito- 1,5-nitrate, an organic nitrate, *e.g.*, Ismo®, Wyeth-Ayerst), nitroglycerin (such as 2,3 propanetriol trinitrate, *e.g.*, Nitrostat® Parke- Davis), verapamil hydrochloride (such as benzeneacetonitrile, (±)-(alpha)[3-[[2-(3,4 dimethoxypheny l)ethyl]methylamino]propyl] -3 ,4-dimethoxy-(alpha)- (1 -methylethyl) hydrochloride, e.g., Covera HS® Extended-Release, Searle), chromonar (which may be prepared as disclosed in US3282938), clonitate (Annalen 1870 155), droprenilamine (which may be prepared as disclosed in DE2521113), lidoflazine (which may be prepared as disclosed in US3267104); prenylamine (which may be prepared as disclosed in US3152173), propatyl nitrate (which may be prepared as disclosed in French Patent No. 1,103,113), mioflazine hydrochloride (1 -Piperazineacetamide, 3-(aminocarbonyl)$_4$-[4,4-bis(4-fluorophenyl)butyl]-N-(2,6- dichlorophenyl)-, dihydrochloride CAS RN 83898-67-3), mixidine (Benzeneethanamine, 3,4- dimethoxy-N-(l-methyl-2-pyrrolidinylidene)- Pyrrolidine, 2-[(3,4-dimethoxyphenethyl)imino]- 1 -methyl- l-Methyl-2- [(3, 4-dimethoxyphenethyl)imino]pyrrolidine CAS RN 27737-38-8), molsidomine (1,2,3-

Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), isosorbide mononitrate (D-Glucitol, 1,4:3,6-dianhydro-, 5-nitrate CAS RN 16051-77-7), erythrityl tetranitrate (1,2,3,4-Butanetetrol, tetranitrate, (2R,3S)-rel-CAS RN 7297-25-8), clonitrate(l,2-Propanediol, 3-chloro-, dinitrate (7CI, 8CI, 9CI) CAS RN 2612-33-1), dipyridamole Ethanol, 2,2',2",2"'-[(4,8-di-l-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis- CAS RN 58-32-2), nicorandil (CAS RN 65141-46-0 3-), pyridinecarboxamide (N-[2-(nitrooxy)ethyl]-Nisoldipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester CAS RN 63675-72-9), nifedipine3,5-Pyridinedicarboxylic acid, l,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester CAS RN 21829-25-4), perhexiline maleate (Piperidine, 2-(2,2-dicyclohexylethyl)-, (2Z)-2-butenedioate (1 :1) CAS RN 6724-53-4), oxprenolol hydrochloride (2-Propanol, 1-[(1-methylethyl)amino]-3-[2-(2-propenyloxy)phenoxy]-, hydrochloride CAS RN 6452-73-9), pentrinitrol (1,3-Propanediol, 2,2-bis[(nitrooxy)methyl]-, mononitrate (ester) CAS RN 1607-17-6), verapamil (Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]- methylamino]propyl]-3, 4-dimethoxy-α-(l -methylethyl)- CAS RN 52-53-9) and the like; angiotensin II receptor antagonists such as, aprosartan, zolasartan, olmesartan, pratosartan, FI6828K, RNH6270, candesartan (1 H-Benzimidazole-7-carboxylic acid, 2-ethoxy-l-[[2'-(lH-tetrazol-5-yl)[l,l'-biphenyl]4-yl]methyl]- CAS RN 139481-59-7), candesartan cilexetil ((+/-)-l-(cyclohexylcarbonyloxy)ethyl-2-ethoxy-l-[[2'-(lH-tetrazol-5-yl)biphenyl-4-yl]-lH-benzimidazole carboxylate, CAS RN 145040-37-5, US5703110 and US5196444), eprosartan (3-[l-4-carboxyphenylmethyl)-2-n-butyl-imidazol-5-yl]-(2-thienylmethyl) propenoic acid, US5185351 and US5650650), irbesartan (2-n-butyl-3- [[2'-(lh-tetrazol-5-yl)biphenyl-4-yl]methyl] 1 ,3-diazazspiro[4,4]non-l-en-4-one, US5270317 and US5352788), losartan (2-N-butyl-4-chloro-5-hydroxymethyl-l-[(2'-(lH-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole, potassium salt, US5138069, US5153197 and US5128355), tasosartan (5,8-dihydro-2,4-dimethyl-8-[(2'-(lH-tetrazol-5-yl)[l,r-biphenyl]4-yl)methyl]-pyrido[2,3-d]pyrimidin-7(6H)-one, US5149699), telmisartan (4'-[(1 ,4-dimethyl-2'-propyl-(2,6'-bi-lH-benzimidazol)-r-yl)]-[1 , 1 '-biphenyl]-2-carboxylic acid, CAS RN 144701-48-4, US5591762), milfasartan, abitesartan, valsartan (Diovan® (Novartis), (S)-N-valeryl-N-[[2'-(lH-tetrazol-5-yl)biphenyl-4-yl)methyl]valine, US5399578), EXP-3137 (2-N-butyl-4-chloro-l-[(2'-(lH-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole-5-carboxylic acid, US5138069, US5153197 and US5128355), 3-(2'-(tetrazol-

5-yl)-l,r-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, 4'[2-ethyl-4-methyl-6-(5,6,7,8-tetrahydroimidazo[l,2-a]pyridin-2-yl]-benzimidazol-l-yl]-methyl]-l,r-biphenyl]-2- carboxylic acid, 2-butyl-6-(l-methoxy-l-methylethyl)-2-[2'-)lH-tetrazol-5-yl)biphenyl-4-ylmethyl] guinazolin-4(3H)-one, 3 - [2 ' -carboxybiphenyl-4-yl)methyl] -2-cyclopropyl-7-methyl- 3H-imidazo[4,5-b]pyridine, 2-butyl-4-chloro-l-[(2'-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-carboxylic acid, 2-butyl-4-chloro-l-[[2'-(lH-tetrazol-5- yl) [1 , 1 ' -biphenyl] -4-yl]methyl]- 1 H-imidazole-5 -carboxylic acid- 1 -(ethoxycarbonyl-oxy)ethyl ester potassium salt, dipotassium 2-butyl-4-(methylthio)-l-[[2-[[[(propylamino)carbonyl]amino]-sulfonyl](l,l '-biphenyl)-4-yl]methyl]-l H-imidazole-5 -carboxylate, methyl-2-[[4-butyl-2-methyl-6-oxo-5-[[2'-(lH-tetrazol-5-yl)-[l,l '-biphenyl]-4-yl]methyl]-l-(6H)- pyrimidinyl]methyl]-3-thiophencarboxylate, 5-[(3,5-dibutyl-lH-l,2,4-triazol-l-yl)methyl]-2-[2- (1 H-tetrazol-5 -ylphenyl)]pyridine, 6-butyl-2-(2-phenylethyl)-5 [[2'-(1 H-tetrazol-5 -yl)[1,1 '- biphenyl]-4-methyl]pyrimidin-4-(3H)-one D,L lysine salt, 5-methyl-7-n-propyl-8-[[2'-(lH- tetrazol-5-yl)biphenyl-4-yl]methyl]-[1 ,2,4]-triazolo[1 ,5-c]pyrimidin-2(3H)-one, 2,7-diethyl-5- [[2'-(5-tetrazoly)biphenyl-4-yl]methyl]-5H-pyrazolo[l,5-b][l,2,4]triazole potassium salt, 2-[2- butyl-4,5-dihydro-4-oxo-3-[2'-(lH-tetrazol-5-yl)-4-biphenylmethyl]-3H-imidazol[4,5- c]pyridine-5-ylmethyl]benzoic acid, ethyl ester, potassium salt, 3-methoxy-2,6-dimethyl-4- [[2'(lH-tetrazol-5-yl)-l,l '-biphenyl-4-yl]methoxy]pyridine, 2-ethoxy-l-[[2'-(5-oxo-2,5-dihydro- 1 ,2,4-oxadiazol-3 -yl)biphenyl-4-yl]methyl] - 1 H-benzimidazole-7-carboxylic acid, 1 - [N-(2 ' -(1 H- tetrazol-5-yl)biphenyl-4-yl-methyl)-N-valerolylaminomethyl)cyclopentane- 1 -carboxylic acid, 7- methyl-2n-propyl-3-[[2' lH-tetrazol-5-yl)biphenyl-4-yl]methyl]-3H-imidazo[4,5-6]pyridine, 2- [5-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine-3-yl)methyl]-2-quinolinyl]sodium benzoate, 2-butyl-6-chloro-4-hydroxymethyl-5 -methyl-3 -[[2'-(l H-tetrazol-5 -yl)biphenyl-4-yl]methyl]pyridine, 2- [[[2-butyl- 1 - [(4-carboxyphenyl)methyl] - 1 H-imidazol-5 -yl]methyl]amino]benzoic acid tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-6-one, 4(S)- [4-(carboxymethyl)phenoxy]-N-[2(R)-[4-(2-sulfobenzamido)imidazol- 1 -yl]octanoyl]-L-proline, 1 - (2,6-dimethylphenyl)-4-butyl-l,3-dihydro-3-[[6-[2-(lH-tetrazol-5-yl)phenyl]-3-pyridinyl]methyl]-2H-imidazol-2-one, 5 ,8-ethano-5 ,8-dimethyl-2-n-propyl-5 ,6,7,8-tetrahydro-1 - [[2'(lH-tetrazol-5-yl)biphenyl-4-yl]methyl]-lH,4H-l,3,4a,8a-tetrazacyclopentanaphthalene-9-one, 4-[l-[2'-(l,2,3,4-tetrazol-5-yl)biphen-4-yl)methylamino]-5,6,7,8-tetrahydro-2-trifylquinazoline, 2-(2-chlorobenzoyl)imino-5-ethyl-3-[2'-(lH-tetrazole-5-yl)biphenyl-4-

yl)methyl-l,3,4-thiadiazoline, 2-[5-ethyl-3-[2-(lH-tetrazole-5-yl)biphenyl-4-yl]methyl-l,3,4-thiazoline-2-ylidene]aminocarbonyl-l-cyclopentencarboxylic acid dipotassium salt, and 2-butyl-4-[N-methyl-N-(3 -methylcrotonoyl)amino] - 1 - [[2 ' -(1 H-tetrazol-5 -yl)biphenyl-4-yl]methyl]- 1 H- imidzole-5 -carboxylic acid 1-ethoxycarbonyloxyethyl ester, those disclosed in patent publications EP475206, EP497150, EP539086, EP539713, EP535463, EP535465, EP542059, EP497121, EP535420, EP407342, EP415886, EP424317, EP435827, EP433983, EP475898, EP490820, EP528762, EP324377, EP323841, EP420237, EP500297, EP426021, EP480204, EP429257, EP430709, EP434249, EP446062, EP505954, EP524217, EP514197, EP514198, EP514193, EP514192, EP450566, EP468372, EP485929, EP503162, EP533058, EP467207 EP399731, EP399732, EP412848, EP453210, EP456442, EP470794, EP470795, EP495626, EP495627, EP499414, EP499416, EP499415, EP511791, EP516392, EP520723, EP520724, EP539066, EP438869, EP505893, EP530702, EP400835, EP400974, EP401030, EP407102, EP411766, EP409332, EP412594, EP419048, EP480659, EP481614, EP490587, EP467715, EP479479, EP502725, EP503838, EP505098, EP505111 EP513,979 EP507594, EP510812, EP511767, EP512675, EP512676, EP512870, EP517357, EP537937, EP534706, EP527534, EP540356, EP461040, EP540039, EP465368, EP498723, EP498722, EP498721, EP515265, EP503785, EP501892, EP519831, EP532410, EP498361, EP432737, EP504888, EP508393, EP508445, EP403159, EP403158, EP425211, EP427463, EP437103, EP481448, EP488532, EP501269, EP500409, EP540400, EP005528, EP028834, EP028833, EP411507, EP425921, EP430300, EP434038, EP442473, EP443568, EP445811, EP459136, EP483683, EP518033, EP520423, EP531876, EP531874, EP392317, EP468470, EP470543, EP502314, EP529253, EP543263, EP540209, EP449699, EP465323, EP521768, EP415594, WO92/14468, WO93/08171, WO93/08169, WO91/00277, WO91/00281, WO91/14367, WO92/00067, WO92/00977, WO92/20342, WO93/04045, WO93/04046, WO91/15206, WO92/14714, WO92/09600, WO92/16552, WO93/05025, WO93/03018, WO91/07404, WO92/02508, WO92/13853, WO91/19697, WO91/11909, WO91/12001, WO91/11999, WO91/15209, WO91/15479, WO92/20687, WO92/20662, WO92/20661, WO93/01177, WO91/14679, WO91/13063, WO92/13564, WO91/17148, WO91/18888, WO91/19715, WO92/02257, WO92/04335, WO92/05161, WO92/07852, WO92/15577, WO93/03033, WO91/16313, WO92/00068, WO92/02510, WO92/09278, WO9210179, WO92/10180, WO92/10186, WO92/10181, WO92/10097, WO92/10183, WO92/10182, WO92/10187, WO92/10184,

WO92/10188, WO92/10180, WO92/10185, WO92/20651, WO93/03722, WO93/06828, WO93/03040, WO92/19211, WO92/22533, WO92/06081, WO92/05784, WO93/00341, WO92/04343, WO92/04059, US5104877, US5187168, US5149699, US5185340, US4880804, US5138069, US4916129, US5153197, US5173494, US5137906, US5155126, US5140037, US5137902, US5157026, US5053329, US5132216, US5057522, US5066586, US5089626, US5049565, US5087702, US5124335, US5102880, US5128327, US5151435, US5202322, US5187159, US5198438, US5182288, US5036048, US5140036, US5087634, US5196537, US5153347, US5191086, US5190942, US5177097, US5212177, US5208234, US5208235, US5212195, US5130439, US5045540, US5041152, and US5210204, and pharmaceutically acceptable salts and esters thereof; α/β adrenergic blockers such as nipradilol, arotinolol, amosulalol, bretylium tosylate (CAS RN: 61-75-6), dihydroergtamine mesylate (such as ergotaman-3', 6',18-trione,9,-10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-,(5'(α))-, monomethanesulfonate, *e.g.*, DHE 45® Injection, Novartis), carvedilol (such as (±)-l-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl] amino] -2-propanol, *e.g.*, Coreg®, SmithKline Beecham), labetalol (such as 5-[l-hydroxy-2-[(l-methyl-3-phenylpropyl) amino] ethyl]salicylamide monohydrochloride, *e.g.*, Normodyne®, Schering), bretylium tosylate (Benzenemethanaminium, 2-bromo-N-ethyl-N,N-dimethyl-, salt with 4-methylbenzenesulfonic acid (1 :1) CAS RN 61-75-6), phentolamine mesylate (Phenol, 3-[[(4,5-dihydro-lH-imidazol-2-yl)methyl](4-methylphenyl)amino]-, monomethanesulfonate (salt) CAS RN 65-28-1), solypertine tartrate (5H-l,3-Dioxolo[4,5-f]indole, 7-[2-[4-(2-methoxyphenyl)-l-piperazinyl]ethyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1 :1) CAS RN 5591-43-5), zolertine hydrochloride (Piperazine, l-phenyl4-[2-(lH-tetrazol-5-yl)ethyl]-, monohydrochloride (8Cl, 9Cl) CAS RN 7241-94-3) and the like; α adrenergic receptor blockers, such as alfuzosin (CAS RN: 81403-68-1), terazosin, urapidil, prazosin (Minipress®), tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, XENOlO, fenspiride hydrochloride (which may be prepared as disclosed in US3399192), proroxan (CAS RN 33743-96-3), and labetalol hydrochloride and combinations thereof; α 2 agonists such as methyldopa, methyldopa HCL, lofexidine, tiamenidine, moxonidine, rilmenidine, guanobenz, and the like; aldosterone inhibitors, and the like; renin inhibitors including Aliskiren (SPPlOO; Novartis/Speedel); angiopoietin-2-binding agents such as those disclosed in WO03/030833; anti-angina agents such as ranolazine (hydrochloride 1-Piperazineacetamide, N-(2,6- dimethylphenyl)-4-[2-hydroxy-3-

(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635- 56-6), betaxolol hydrochloride (2-Propanol, l-[4-[2 (cyclopropylmethoxy)ethyl]phenoxy]-3-[(l- methylethyl)amino]-, hydrochloride CAS RN 63659-19-8), butoprozine hydrochloride (Methanone, [4-[3(dibutylamino)propoxy]phenyl](2-ethyl-3-indolizinyl)-, monohydrochloride CAS RN 62134-34-3), cinepazet maleatel-Piperazineacetic acid, 4-[l-oxo-3-(3,4,5- trimethoxyphenyl)-2-propenyl]-, ethyl ester, (2Z)-2-butenedioate (1 :1) CAS RN 50679-07-7), tosifen (Benzenesulfonamide, 4-methyl-N-[[[(lS)-l-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184), verapamilhydrochloride (Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3 ,4-dimethoxy-α-(1 -methylethyl)-, monohydrochloride CAS RN 152-114), molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), and ranolazine hydrochloride (1 -Piperazineacetamide, N-(2,6-dimethylphenyl)$_4$-[2-hydroxy-3-(2-meth-oxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6); tosifen (Benzenesulfonamide, 4-methyl-N-[[[(lS)-l-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184); adrenergic stimulants such as guanfacine hydrochloride (such as N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride, *e.g.*, Tenex® Tablets available from Robins); methyldopa-hydrochlorothiazide (such as levo-3-(3,4-dihydroxyphenyl)-2-methylalanine) combined with Hydrochlorothiazide (such as 6-chloro-3,4-dihydro-2H -l,2,4-benzothiadiazine-7- sulfonamide 1,1-dioxide, *e.g.*, the combination as, e.g., Aldoril® Tablets available from Merck), methyldopa-chlorothiazide (such as 6-chloro-2H-l, 2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and methyldopa as described above, e.g., Aldoclor®, Merck), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride and chlorthalidone (such as 2-chloro-5-(l-hydroxy-3-oxo-l-isoindolinyl) benzenesulfonamide), *e.g.*, Combipres®, Boehringer Ingelheim), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride, e.g., Catapres®, Boehringer Ingelheim), clonidine (lH-Imidazol-2-amine, N-(2,6-dichlorophenyl)4,5-dihydro-CAS RN 4205-90-7), Hyzaar (Merck; a combination of losartan and hydrochlorothiazide), Co-Diovan (Novartis; a combination of valsartan and hydrochlorothiazide, Lotrel (Novartis; a combination of benazepril and amlodipine) and Caduet (Pfizer; a combination of amlodipine and atorvastatin), and those agents disclosed in US20030069221.

Agents for the Treatment of Respiratory Disorders

The GCRA peptides described herein can be used in combination therapy with one or more of the following agents useful in the treatment of respiratory and other disorders including but not limited to: (1) β-agonists including but not limited to : albuterol (PRO VENTIL® , S ALBUT AMOl® , VENTOLIN®), bambuterol, bitoterol, clenbuterol, fenoterol, formoterol, isoetharine (BRONKOSOL®, BRONKOMETER®), metaproterenol (ALUPENT®, METAPREL®), pirbuterol (MAXAIR®), reproterol, rimiterol, salmeterol, terbutaline (BRETHAIRE®, BRETHINE®, BRICANYL®), adrenalin, isoproterenol (ISUPREL®), epinephrine bitartrate (PRIMATENE®), ephedrine, orciprenline, fenoterol and isoetharine; (2) steroids, including but not limited to beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, bunedoside, butixocort, dexamethasone, flunisolide, fluocortin, fluticasone, hydrocortisone, methyl prednisone, mometasone, predonisolone, predonisone, tipredane, tixocortal, triamcinolone, and triamcinolone acetonide; (3) β2-agonist-corticosteroid combinations [*e.g.*, salmeterol-fluticasone (AD V AIR®), formoterol-budesonid (S YMBICORT®)] ; (4) leukotriene D4 receptor antagonists/leukotriene antagonists/LTD4 antagonists (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between leukotrienes and the Cys LTI receptor) including but not limited to: zafhiukast, montelukast, montelukast sodium (SINGULAIR®), pranlukast, iralukast, pobilukast, SKB-106,203 and compounds described as having LTD4 antagonizing activity described in U.S. Patent No. 5,565,473; (5) 5 -lipoxygenase inhibitors and/or leukotriene biosynthesis inhibitors [e.g., zileuton and BAY1005 (CA registry 128253-31-6)]; (6) histamine Hl receptor antagonists/antihistamines (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between histamine and its receptor) including but not limited to: astemizole, acrivastine, antazoline, azatadine, azelastine, astamizole, bromopheniramine, bromopheniramine maleate, carbinoxamine, carebastine, cetirizine, chlorpheniramine, chloropheniramine maleate, cimetidine clemastine, cyclizine, cyproheptadine, descarboethoxyloratadine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine succinate, doxylarnine, ebastine, efletirizine, epinastine, famotidine, fexofenadine, hydroxyzine, hydroxyzine, ketotifen, levocabastine, levocetirizine, levocetirizine, loratadine, meclizine, mepyramine, mequitazine, methdilazine, mianserin, mizolastine, noberastine, norasternizole, noraztemizole, phenindamine, pheniramine, picumast,

promethazine, pynlamine, pyrilamine, ranitidine, temelastine, terfenadine, trimeprazine, tripelenamine, and triprolidine; (7) an anticholinergic including but not limited to: atropine, benztropine, biperiden, flutropium, hyoscyamine (e.g. Levsin®; Levbid®; Levsin/SL®, Anaspaz®, Levsinex timecaps®, NuLev®), ilutropium, ipratropium, ipratropium bromide, methscopolamine, oxybutinin, rispenzepine, scopolamine, and tiotropium; (8) an anti-tussive including but not limited to: dextromethorphan, codeine, and hydromorphone; (9) a decongestant including but not limited to: pseudoephedrine and phenylpropanolamine; (10) an expectorant including but not limited to: guafenesin, guaicolsulfate, terpin, ammonium chloride, glycerol guaicolate, and iodinated glycerol; (11) a bronchodilator including but not limited to: theophylline and aminophylline; (12) an anti-inflammatory including but not limited to: fluribiprofen, diclophenac, indomethacin, ketoprofen, S-ketroprophen, tenoxicam; (13) a PDE (phosphodiesterase) inhibitor including but not limited to those disclosed herein; (14) a recombinant humanized monoclonal antibody [e.g. xolair (also called omalizumab), rhuMab, and talizumab]; (15) a humanized lung surfactant including recombinant forms of surfactant proteins SP-B, SP-C or SP-D [e.g. SURFAXIN®, formerly known as dsc-104 (Discovery Laboratories)], (16) agents that inhibit epithelial sodium channels (ENaC) such as amiloride and related compounds; (17) antimicrobial agents used to treat pulmonary infections such as acyclovir, amikacin, amoxicillin, doxycycline, trimethoprin sulfamethoxazole, amphotericin B, azithromycin, clarithromycin, roxithromycin, clarithromycin, cephalosporins(ceffoxitin, cefmetazole etc), ciprofloxacin, ethambutol, gentimycin, ganciclovir, imipenem, isoniazid, itraconazole, penicillin, ribavirin, rifampin, rifabutin,amantadine, rimantidine, streptomycin, tobramycin, and vancomycin; (18) agents that activate chloride secretion through Ca++ dependent chloride channels (such as purinergic receptor (P2Y(2) agonists); (19) agents that decrease sputum viscosity, such as human recombinant DNase 1, (Pulmozyme®); (20) nonsteroidal anti-inflammatory agents (acemetacin, acetaminophen, acetyl salicylic acid, alclofenac, alminoprofen, apazone, aspirin, benoxaprofen, bezpiperylon, bucloxic acid, carprofen, clidanac, diclofenac, diclofenac, diflunisal, diflusinal, etodolac, fenbufen, fenbufen, fenclofenac, fenclozic acid, fenoprofen, fentiazac, feprazone, flufenamic acid, flufenisal, flufenisal, fluprofen, flurbiprofen, flurbiprofen, furofenac, ibufenac, ibuprofen, indomethacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketoprofen, ketorolac, meclofenamic acid, meclofenamic acid, mefenamic acid, mefenamic acid, miroprofen, mofebutazone,

nabumetone oxaprozin, naproxen, naproxen, niflumic acid , oxaprozin, oxpinac, oxyphenbutazone, phenacetin, phenylbutazone, phenylbutazone, piroxicam, piroxicam, pirprofen, pranoprofen, sudoxicam, tenoxican, sulfasalazine, sulindac, sulindac, suprofen, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, tolmetin, zidometacin, zomepirac, and zomepirac); and (21) aerosolized antioxidant therapeutics such as S-Nitrosoglutathione.

Anti-obesity agents

The GCRA peptides described herein can be used in combination therapy with an anti-obesity agent. Suitable such agents include, but are not limited to: 1 lβ HSD-I (11-beta hydroxy steroid dehydrogenase type 1) inhibitors, such as BVT 3498, BVT 2733, 3-(l-adamantyl)-4-ethyl-5-(ethylthio)- 4H-l,2,4-triazole, 3-(l-adamantyl)-5-(3,4,5- trimethoxyphenyl)-4-methyl-4H-l,2,4-triazole, 3- adamantanyl-4,5,6,7,8,9,10,11,12,3a- decahydro-l,2,4-triazolo[4,3-a][l l]annulene, and those compounds disclosed in WO01/90091, WOO 1/90090, WOO 1/90092 and WO02/072084; 5HT antagonists such as those in WO03/037871, WO03/037887, and the like; 5HTIa modulators such as carbidopa, benserazide and those disclosed in US6207699, WO03/031439, and the like; 5HT2c (serotonin receptor 2c) agonists, such as BVT933, DPCA37215, IK264, PNU 22394, WAY161503, R-1065, SB 243213 (Glaxo Smith Kline) and YM 348 and those disclosed in US3914250, WO00/77010, WO02/36596, WO02/48124, WO02/10169, WO01/66548, WO02/44152, WO02/51844, WO02/40456, and WO02/40457; 5HT6 receptor modulators, such as those in WO03/030901, WO03/035061, WO03/039547, and the like; acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al, Obesity Research, 9:202-9 (2001) and Japanese Patent Application No. JP 2000256190; anorectic bicyclic compounds such as 1426 (Aventis) and 1954 (Aventis), and the compounds disclosed in WO00/18749, WO01/32638, WO01/62746, WO01/62747, and WO03/015769; CB 1 (cannabinoid-1 receptor) antagonist/inverse agonists such as rimonabant (Acomplia; Sanofi), SR-147778 (Sanofi), SR-141716 (Sanofi), BAY 65-2520 (Bayer), and SLV 319 (Solvay), and those disclosed in patent publications US4973587, US5013837, US5081122, US5112820, US5292736, US5532237, US5624941, US6028084, US6509367, US6509367, WO96/33159, WO97/29079, WO98/31227, WO98/33765, WO98/37061, WO98/41519, WO98/43635, WO98/43636, WO99/02499, WO00/10967, WO00/10968, WO01/09120, WO01/58869, WO01/64632,

WO01/64633, WO01/64634, WO01/70700, WO01/96330, WO02/076949, WO03/006007, WO03/007887, WO03/020217, WO03/026647, WO03/026648, WO03/027069, WO03/027076, WO03/027114, WO03/037332, WO03/040107, WO03/086940, WO03/084943 and EP658546; CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771 (GSK), JMV-180, A-71378, A-71623 and SR146131 (Sanofi), and those described in US5739106; CNTF (Ciliary neurotrophic factors), such as GI- 181771 (Glaxo-SmithKline), SRI 46131 (Sanofi Synthelabo), butabindide, PD 170,292, and PD 149164 (Pfizer); CNTF derivatives, such as Axokine® (Regeneron), and those disclosed in WO94/09134, WO98/22128, and WO99/43813; dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, P 3298, TSL 225 (tryptophyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), TMC-2A/2B/2C, CD26 inhibtors, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) and the compounds disclosed patent publications. WO99/38501, WO99/46272, WO99/67279 (Probiodrug), WO99/67278 (Probiodrug), WO99/61431 (Probiodrug), WO02/083128, WO02/062764, WO03/000180, WO03/000181, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/004498, WO03/004496,WO03/017936, WO03/024942, WO03/024965, WO03/033524, WO03/037327 and EP1258476; growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK- 0677 (Merck), SM-130686, CP-424391 (Pfizer), LY 444,711 (Eli Lilly), L-692,429 and L- 163,255, and such as those disclosed in USSN 09/662448, US provisional application 60/203335, US6358951, US2002049196, US2002/022637, WO01/56592 and WO02/32888; H3 (histamine H3) antagonist/inverse agonists, such as thioperamide, 3-(IH-imidazol-4- yl)propyl N-(4-pentenyl)carbamate), clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and A331440, O-[3-(IH-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-32 (2001), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)), substituted N- phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., J. Med. Chem.. 43:3335-43 (2000)) and histamine H3 receptor modulators such as those disclosed in WO02/15905, WO03/024928 and WO03/024929;

leptin derivatives, such as those disclosed in US5552524, US5552523, US5552522, US5521283, WO96/23513, WO96/23514, WO96/23515, WO96/23516, WO96/23517, WO96/23518, WO96/23519, and WO96/23520; leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); lipase inhibitors, such as tetrahydrolipstatin (orlistat/Xenical®), Triton WR1 339, RHC80267, lipstatin, teasaponin, diethylumbelliferyl phosphate, FL-386, WAY-121898, Bay-N-3176, valilactone, esteracin, ebelactone A, ebelactone B, and RHC 80267, and those disclosed in patent publications WO01/77094, US4598089, US4452813, USUS5512565, US5391571, US5602151, US4405644, US4189438, and US4242453; lipid metabolism modulators such as maslinic acid, erythrodiol, ursolic acid uvaol, betulinic acid, betulin, and the like and compounds disclosed in WO03/011267; Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME-10142, ME-10145, and HS-131 (Melacure), and those disclosed in PCT publication Nos. WO99/64002, WO00/74679, WOO 1/991752, WOO 1/25192, WOO 1/52880, WOO 1/74844, WOO 1/70708, WO01/70337, WO01/91752, WO02/059095, WO02/059107, WO02/059108, WO02/059117, WO02/06276, WO02/12166, WO02/11715, WO02/12178, WO02/15909, WO02/38544, WO02/068387, WO02/068388, WO02/067869, WO02/081430, WO03/06604, WO03/007949, WO03/009847, WO03/009850, WO03/013509, and WO03/031410; Mc5r (melanocortin 5 receptor) modulators, such as those disclosed in WO97/19952, WO00/15826, WO00/15790, US20030092041; melanin-concentrating hormone 1 receptor (MCHR) antagonists, such as T-226296 (Takeda), SB 568849, SNP-7941 (Synaptic), and those disclosed in patent publications WOO 1/21169, WO01/82925, WO01/87834, WO02/051809, WO02/06245, WO02/076929, WO02/076947, WO02/04433, WO02/51809, WO02/083134, WO02/094799, WO03/004027, WO03/13574, WO03/15769, WO03/028641, WO03/035624, WO03/033476, WO03/033480, JP13226269, and JP1437059; mGluR5 modulators such as those disclosed in WO03/029210, WO03/047581, WO03/048137, WO03/051315, WO03/051833, WO03/053922, WO03/059904, and the like; serotoninergic agents, such as fenfluramine (such as Pondimin® (Benzeneethanamine, N-ethyl- alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Robbins), dexfenfluramine (such as Redux® (Benzeneethanamine, N-ethyl-alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Interneuron) and sibutramine ((Meridia®, Knoll/Reductil™) including racemic mixtures, as optically pure isomers (+) and (-), and pharmaceutically acceptable salts, solvents, hydrates, clathrates and prodrugs thereof including sibutramine

hydrochloride monohydrate salts thereof, and those compounds disclosed in US4746680, US4806570, and US5436272, US20020006964, WOO 1/27068, and WOO 1/62341; NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; NPY 1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI- 264879A, and those disclosed in US6001836, WO96/14307, WO01/23387, WO99/51600, WO01/85690, WO01/85098, WO01/85173, and WO01/89528; NPY5 (neuropeptide Y Y5) antagonists, such as 152,804, GW-569180A, GW-594884A, GW-587081X, GW-548118X, FR235208, FR226928, FR240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, LY-366377, PD-160170, SR- 120562A, SR-120819A, JCF-104, and H409/22 and those compounds disclosed in patent publications US6140354, US6191160, US6218408, US6258837, US6313298, US6326375, US6329395, US6335345, US6337332, US6329395, US6340683, EP01010691, EP-01044970, WO97/19682, WO97/20820, WO97/20821, WO97/20822, WO97/20823, WO98/27063, WO00/107409, WO00/185714, WO00/185730, WO00/64880, WO00/68197, WO00/69849, WO/0113917, WO01/09120, WO01/14376, WO01/85714, WO01/85730, WO01/07409, WO01/02379, WO01/23388, WO01/23389, WOO 1/44201, WO01/62737, WO01/62738, WO01/09120, WO02/20488, WO02/22592, WO02/48152, WO02/49648, WO02/051806, WO02/094789, WO03/009845, WO03/014083, WO03/022849, WO03/028726 and Norman et al, J. Med. Chem. 43:4288-4312 (2000); opioid antagonists, such as nalmefene (REVEX ®), 3-methoxynaltrexone, methylnaltrexone, naloxone, and naltrexone (e.g. PT901; Pain Therapeutics, Inc.) and those disclosed in US20050004155 and WO00/21509; orexin antagonists, such as SB-334867-A and those disclosed in patent publications WO01/96302, WO01/68609, WO02/44172, WO02/51232, WO02/51838, WO02/089800, WO02/090355, WO03/023561, WO03/032991, and WO03/037847; PDE inhibitors (e.g. compounds which slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and cGMP; possible PDE inhibitors are primarily those substances which are to be numbered among the class consisting of the PDE3 inhibitors, the class consisting of the PDE4 inhibitors and/or the class consisting of the PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors) such as those disclosed in patent publications DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801,

DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EPOI 12987, EPOI 16948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, US4963561, US5141931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DEI 116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6331543, US20050004222 (including those disclosed in formulas I- XIII and paragraphs 37-39, 85-0545 and 557-577), WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399, as well as PDE5 inhibitors (such as RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra™)), PDE4 inhibitors (such as etazolate, ICI63197, RP73401, imazolidinone (RO-20-1724), MEM 1414 (R1533/R1500; Pharmacia Roche), denbufylline, rolipram, oxagrelate, nitraquazone, Y-590, DH-6471, SKF-94120, motapizone, lixazinone, indolidan, olprinone, atizoram, KS-506-G, dipamfylline, BMY-43351, atizoram, arofylline, filaminast, PDB-093, UCB-29646, CDP-840, SKF-107806, piclamilast, RS-17597, RS-25344- 000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, mopidamol, anagrelide, ibudilast, amrinone, pimobendan, cilostazol, quazinone and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide, PDE3 inhibitors (such as ICI153, 100, bemorandane (RWJ 22867), MCI-154, UD-CG 212, sulmazole, ampizone, cilostamide, carbazeran, piroximone, imazodan, CI-930, siguazodan, adibendan,

saterinone, SKF-95654, SDZ-MKS-492, 349-U-85, emoradan, EMD-53998, EMD- 57033, NSP-306, NSP-307, revizinone, NM-702, WIN-62582 and WIN-63291, enoximone and milrinone, PDE3/4 inhibitors (such as benafentrine, trequinsin, ORG-30029, zardaverine, L- 686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and tolafentrine) and other PDE inhibitors (such as vinpocetin, papaverine, enprofylline, cilomilast, fenoximone, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®); Neuropeptide Y2 (NPY2) agonists include but are not limited to: polypeptide YY and fragments and variants thereof (e.g. YY3-36 (PYY3-36)(N. Engl. J. Med. 349:941, 2003; IKPEAPGE DASPEELNRY YASLRHYLNL VTRQRY (SEQ ID NO:XXX)) and PYY agonists such as those disclosed in WO02/47712, WO03/026591, WO03/057235, and WO03/027637; serotonin reuptake inhibitors, such as, paroxetine, fluoxetine (Prozac™), fluvoxamine, sertraline, citalopram, and imipramine, and those disclosed in US6162805, US6365633, WO03/00663, WOO 1/27060, and WOO 1/162341; thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in WO02/15845, WO97/21993, WO99/00353, GB98/284425, U.S. Provisional Application No. 60/183,223, and Japanese Patent Application No. JP 2000256190; UCP-I (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5, 6,7,8- tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-l-propenyl]benzoic acid (TTNPB), retinoic acid, and those disclosed in WO99/00123; β3 (beta adrenergic receptor 3) agonists, such as AJ9677/TAK677 (Dainippon/Takeda), L750355 (Merck), CP331648 (Pfizer), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GW 427353, Trecadrine, Zeneca D7114, N-5984 (Nisshin Kyorin), LY-377604 (Lilly), SR 59119A, and those disclosed in US5541204, US5770615, US5491134, US5776983, US488064, US5705515, US5451677, WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753, WO01/74782, WO02/32897, WO03/014113, WO03/016276, WO03/016307, WO03/024948, WO03/024953 and WO03/037881; noradrenergic agents including, but not limited to, diethylpropion (such as Tenuate® (1- propanone, 2-(diethylamino)-l -phenyl-, hydrochloride), Merrell), dextroamphetamine (also known as dextroamphetamine sulfate, dexamphetamine, dexedrine, Dexampex, Ferndex, Oxydess II, Robese, Spancap #1), mazindol ((or 5-(p-chlorophenyl)-2,5-dihydro-3H- imidazo[2,l-a]isoindol-5-ol) such as Sanorex®, Novartis or Mazanor®, Wyeth Ayerst), phenylpropanolamine (or Benzenemethanol, alpha-(l-aminoethyl)-, hydrochloride), phentermine ((or Phenol, 3-[[4,5-duhydro-lH-imidazol-2-yl)ethyl](4-

methylpheny-l)amino], monohydrochloride) such as Adipex-P®, Lemmon, FASTIN®, Smith-Kline Beecham and Ionamin®, Medeva), phendimetrazine ((or (2S,3S)-3,4-Dimethyl-2phenylmorpholine L-(+)- tartrate (1 :1)) such as Metra® (Forest) , Plegine® (Wyeth- Ay erst), Prelu-2® (Boehringer Ingelheim), and Statobex® (Lemmon), phendamine tartrate (such as Thephorin® (2,3,4,9- Tetrahydro-2-methyl-9-phenyl-lH-indenol[2,l-c]pyridine L-(+)-tartrate (1 :1)), Hoffmann- LaRoche), methamphetamine (such as Desoxyn®, Abbot ((S)-N, (alpha)-dimethylbenzeneethanamine hydrochloride)), and phendimetrazine tartrate (such as Bontril® Slow-Release Capsules, Amarin (-3,4-Dimethyl-2-phenylmorpholine Tartrate); fatty acid oxidation upregulator/inducers such as Famoxin® (Genset); monamine oxidase inhibitors including but not limited to befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, toloxatone, pirlindol, amiflamine, sercloremine, bazinaprine, lazabemide, milacemide, caroxazone and other certain compounds as disclosed by WO01/12176; and other anti-obesity agents such as 5HT-2 agonists, ACC (acetyl-CoA carboxylase) inhibitors such as those described in WO03/072197, alpha-lipoic acid (alpha-LA), AOD9604, appetite suppressants such as those in WO03/40107, ATL-962 (Alizyme PLC), benzocaine, benzphetamine hydrochloride (Didrex), bladderwrack (focus vesiculosus), BRS3 (bombesin receptor subtype 3) agonists, bupropion, caffeine, CCK agonists, chitosan, chromium, conjugated linoleic acid, corticotropin-releasing hormone agonists, dehydroepiandrosterone, DGATl (diacylglycerol acyltransferase 1) inhibitors, DGAT2 (diacylglycerol acyltransferase 2) inhibitors, dicarboxylate transporter inhibitors, ephedra, exendin-4 (an inhibitor of glp-1) FAS (fatty acid synthase) inhibitors (such as Cerulenin and C75), fat resorption inhibitors (such as those in WO03/053451, and the like), fatty acid transporter inhibitors, natural water soluble fibers (such as psyllium, plantago, guar, oat, pectin), galanin antagonists, galega (Goat's Rue, French Lilac), garcinia cambogia, germander (teucrium chamaedrys), ghrelin antibodies and ghrelin antagonists (such as those disclosed in WO01/87335, and WO02/08250), polypeptide hormones and variants thereof which affect the islet cell secretion, such as the hormones of the secretin/gastric inhibitory polypeptide (GIP)/vasoactive intestinal polypeptide (VIP)/pituitary adenylate cyclase activating polypeptide (PACAP)/glucagon-like polypeptide II (GLP- II)/glicentin/glucagon gene family and/or those of the adrenomedullin/amylin/calcitonin gene related polypeptide (CGRP) gene family includingGLP-1 (glucagon- like polypeptide 1) agonists (e.g. (1) exendin-4, (2) those GLP-1 molecules described in US20050130891 including GLP- 1(7-34), GLP-l(7-35), GLP-l(7-36) or

GLP-l(7-37) in its C-terminally carboxylated or amidated form or as modified GLP-1 polypeptides and modifications thereof including those described in paragraphs 17-44 of US20050130891, and derivatives derived from GLP-l-(7- 34)COOH and the corresponding acid amide are employed which have the following general formula: R-NH-HAEGTFTSDVSYLEGQAAKEFIAWLVK-$CONH_2$ wherein R=H or an organic compound having from 1 to 10 carbon atoms. Preferably, R is the residue of a carboxylic acid. Particularly preferred are the following carboxylic acid residues: formyl, acetyl, propionyl, isopropionyl, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert- butyl.) and glp-1 (glucagon-like polypeptide- 1), glucocorticoid antagonists, glucose transporter inhibitors, growth hormone secretagogues (such as those disclosed and specifically described in US5536716), interleukin-6 (IL-6) and modulators thereof (as in WO03/057237, and the like), L- carnitine, Mc3r (melanocortin 3 receptor) agonists, MCH2R (melanin concentrating hormone 2R) agonist/antagonists, melanin concentrating hormone antagonists, melanocortin agonists (such as Melanotan II or those described in WO 99/64002 and WO 00/74679), nomame herba, phosphate transporter inhibitors, phytopharm compound 57 (CP 644,673), pyruvate, SCD-I (stearoyl-CoA desaturase-1) inhibitors, T71 (Tularik, Inc., Boulder CO), Topiramate (Topimax®, indicated as an anti-convulsant which has been shown to increase weight loss), transcription factor modulators (such as those disclosed in WO03/026576), β-hydroxy steroid dehydrogenase- 1 inhibitors (β -HSD-I), β-hydroxy-β-methylbutyrate, p57 (Pfizer), Zonisamide (Zonegran™, indicated as an anti-epileptic which has been shown to lead to weight loss), and the agents disclosed in US20030119428 paragraphs 20-26.

Anti-Diabetic Agents

The GCRA peptides described herein can be used in therapeutic combination with one or more anti-diabetic agents, including but not limited to: PPARγ agonists such as glitazones (*e.g.*, WAY-120,744, AD 5075, balaglitazone, ciglitazone, darglitazone (CP-86325, Pfizer), englitazone (CP-68722, Pfizer), isaglitazone (MIT/J&J), MCC- 555 (Mitsibishi disclosed in US5594016), pioglitazone (such as such as Actos™ pioglitazone; Takeda), rosiglitazone (Avandia™;Smith Kline Beecham), rosiglitazone maleate, troglitazone (Rezulin®, disclosed in US4572912), rivoglitazone (CS-Ol 1, Sankyo), GL-262570 (Glaxo Welcome), BRL49653 (disclosed in WO98/05331), CLX-0921, 5-BTZD, GW-0207, LG- 100641, JJT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/Pfizer), NN-2344 (Dr. Reddy/NN), YM-

440 (Yamanouchi), LY-300512, LY-519818, R483 (Roche), T131 (Tularik), and the like and compounds disclosed in US4687777, US5002953, US5741803, US5965584, US6150383, US6150384, US6166042, US6166043, US6172090, US6211205, US6271243, US6288095, US6303640, US6329404, US5994554, W097/10813, WO97/27857, WO97/28115, WO97/28137,WO97/27847, WO00/76488, WO03/000685,WO03/027112,WO03/035602, WO03/048130, WO03/055867, and pharmaceutically acceptable salts thereof; biguanides such as metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride, such as Glucophage™, Bristol-Myers Squibb); metformin hydrochloride with glyburide, such as Glucovance™, Bristol-Myers Squibb); buformin (Imidodicarbonimidic diamide, N-butyl-); etoformine (l-Butyl-2-ethylbiguanide, Schering A. G.); other metformin salt forms (including where the salt is chosen from the group of, acetate, benzoate, citrate, ftimarate, embonate, chlorophenoxyacetate, glycolate, palmoate, aspartate, methanesulphonate, maleate, parachlorophenoxyisobutyrate, formate, lactate, succinate, sulphate, tartrate, cyclohexanecarboxylate, hexanoate, octanoate, decanoate, hexadecanoate, octodecanoate, benzenesulphonate, trimethoxybenzoate, paratoluenesulphonate, adamantanecarboxylate, glycoxylate, glutarnate, pyrrolidonecarboxylate, naphthalenesulphonate, 1-glucosephosphate, nitrate, sulphite, dithionate and phosphate), and phenformin; protein tyrosine phosphatase- IB (PTP-IB) inhibitors, such as A-401,674, KR 61639, OC- 060062, OC-83839, OC-297962, MC52445, MC52453, ISIS 113715, and those disclosed in WO99/585521, WO99/58518, WO99/58522, WO99/61435, WO03/032916, WO03/032982, WO03/041729, WO03/055883, WO02/26707, WO02/26743, JP2002114768, and pharmaceutically acceptable salts and esters thereof; sulfonylureas such as acetohexamide (*e.g.* Dymelor, Eli Lilly), carbutamide, chlorpropamide (*e.g.* Diabinese®, Pfizer), gliamilide (Pfizer), gliclazide (*e.g.* Diamcron, Servier Canada Inc), glimepiride (*e.g.* disclosed in US4379785, such as Amaryl , Aventis), glipentide, glipizide (*e.g.* Glucotrol or Glucotrol XL Extended Release, Pfizer), gliquidone, glisolamide, glyburide/glibenclamide (*e.g.* Micronase or Glynase Prestab, Pharmacia & Upjohn and Diabeta, Aventis), tolazamide (*e.g.* Tolinase), and tolbutamide (*e.g.* Orinase), and pharmaceutically acceptable salts and esters thereof; meglitinides such as repaglinide (*e.g.* Pranidin®, Novo Nordisk), KAD1229 (PF/Kissei), and nateglinide (*e.g.* Starlix®, Novartis), and pharmaceutically acceptable salts and esters thereof; α glucoside hydrolase inhibitors (or glucoside inhibitors) such as acarbose (*e.g.* Precose™, Bayer disclosed in US4904769), miglitol (such as GLYSET™,

Pharmacia & Upjohn disclosed in US4639436), camiglibose (Methyl 6-deoxy-6-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2- (hydroxymethyl)piperidino]-alpha-D-glucopyranoside, Marion Merrell Dow), voglibose (Takeda), adiposine, emiglitate, pradimicin-Q, salbostatin, CKD-711, MDL-25,637, MDL- 73,945, and MOR 14, and the compounds disclosed in US4062950, US4174439, US4254256, US4701559, US4639436, US5192772, US4634765, US5157116, US5504078, US5091418, US5217877, US51091 and WOO 1/47528 (polyamines); α-amylase inhibitors such as tendamistat, trestatin, and Al -3688, and the compounds disclosed in US4451455, US4623714, and US4273765; SGLT2 inhibtors including those disclosed in US6414126 and US6515117; an aP2 inhibitor such as disclosed in US6548529; insulin secreatagogues such as linogliride, A-4166, forskilin, dibutyrl cAMP, isobutylmethylxanthine (IBMX), and pharmaceutically acceptable salts and esters thereof; fatty acid oxidation inhibitors, such as clomoxir, and etomoxir, and pharmaceutically acceptable salts and esters thereof; A2 antagonists, such as midaglizole, isaglidole, deriglidole, idazoxan, earoxan, and fluparoxan, and pharmaceutically acceptable salts and esters thereof; insulin and related compounds (e.g. insulin mimetics) such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente), Lys-Pro insulin, GLP-I (1-36) amide, GLP-I (73-7) (insulintropin, disclosed in US5614492), LY-315902 (Lilly), GLP-I (7-36)-NH2), AL-401 (Autoimmune), certain compositions as disclosed in US4579730, US4849405, US4963526, US5642868, US5763396, US5824638, US5843866, US6153632, US6191105, and WO 85/05029, and primate, rodent, or rabbit insulin including biologically active variants thereof including allelic variants, more preferably human insulin available in recombinant form (sources of human insulin include pharmaceutically acceptable and sterile formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin™ (human insulin rDNA origin), also see the THE PHYSICIAN'S DESK REFERENCE, 55.sup.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins); non-thiazolidinediones such as JT-501 and farglitazar (GW-2570/GI- 262579), and pharmaceutically acceptable salts and esters thereof; PPARα/γ dual agonists such as AR-HO39242 (Aztrazeneca), GW-409544 (Glaxo-Wellcome), BVT-142, CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297 (Kyorin Merck; 5-[(2,4-Dioxo thiazolidinyl)methyl] methoxy-N-[[4-(trifluoromethyl)phenyl] methyl]benzamide), L-796449, LR-90, MK-0767 (Merck/Kyorin/Banyu), SB 219994, muraglitazar (BMS), tesaglitzar (Astrazeneca), reglitazar

(JTT-501) and those disclosed in WO99/16758, WO99/19313, WO99/20614, WO99/38850, WO00/23415, WO00/23417, WO00/23445, WO00/50414, WO01/00579, WO01/79150, WO02/062799, WO03/004458, WO03/016265, WO03/018010, WO03/033481, WO03/033450, WO03/033453, WO03/043985, WO 031053976, U.S. application Ser. No. 09/664,598, filed Sep. 18, 2000, Murakami et al. Diabetes 47, 1841-1847 (1998), and pharmaceutically acceptable salts and esters thereof; other insulin sensitizing drugs; VPAC2 receptor agonists; GLK modulators, such as those disclosed in WO03/015774; retinoid modulators such as those disclosed in WO03/000249; GSK 3β/GSK 3 inhibitors such as 4-[2-(2-bromophenyl)-4-(4-fluorophenyl-lH-imidazol-5- yl]pyridine and those compounds disclosed in WO03/024447, WO03/037869, WO03/037877, WO03/037891, WO03/068773, EP1295884, EP1295885, and the like; glycogen phosphorylase (HGLPa) inhibitors such as CP-368,296, CP-316,819, BAYR3401, and compounds disclosed in WOO 1/94300, WO02/20530, WO03/037864, and pharmaceutically acceptable salts or esters thereof; ATP consumption promotors such as those disclosed in WO03/007990; TRB3 inhibitors; vanilloid receptor ligands such as those disclosed in WO03/049702; hypoglycemic agents such as those disclosed in WO03/015781 and WO03/040114; glycogen synthase kinase 3 inhibitors such as those disclosed in WO03/035663 agents such as those disclosed in WO99/51225, US20030134890, WO01/24786, and WO03/059870; insulin-responsive DNA binding protein-1 (IRDBP-I) as disclosed in WO03/057827, and the like; adenosine A2 antagonists such as those disclosed in WO03/035639, WO03/035640, and the like; PPARδ agonists such as GW 501516, GW 590735, and compounds disclosed in JP10237049 and WO02/14291; dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, NVP-DPP728A (1- [[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999), P32/98, NVP-LAF-237, P3298, TSL225 (tryptophyl-l,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), valine pyrrolidide, TMC-2A/2B/2C, CD- 26 inhibitors, FE999011, P9310/K364, VIP 0177, DPP4, SDZ 274-444, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) ,and the compounds disclosed in US6395767, US6573287, US6395767 (compounds disclosed include BMS-477118, BMS-471211 and BMS 538,305), WO99/38501, WO99/46272, WO99/67279, WO99/67278, WO99/61431WO03/004498, WO03/004496,

EP1258476, WO02/083128, WO02/062764, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/000180, and WO03/000181; GLP-I agonists such as exendin-3 and exendin-4 (including the 39 aa polypeptide synthetic exendin-4 called Exenatide®), and compounds disclosed in US2003087821 and NZ 504256, and pharmaceutically acceptable salts and esters thereof; peptides including amlintide and Symlin® (pramlintide acetate); and glycokinase activators such as those disclosed in US2002103199 (fused heteroaromatic compounds) and WO02/48106 (isoindolin-1-one-substituted propionamide compounds).

Phosphodiesterase inhibitors

The GCRA peptides described herein can be used in combination therapy with a phosphodiesterase inhibitor. PDE inhibitors are those compounds which slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a relative increase in the intracellular concentration of c AMP and/or cGMP. Possible PDE inhibitors are primarily those substances which are to be numbered among the class consisting of the PDE3 inhibitors, the class consisting of the PDE4 inhibitors and/or the class consisting of the PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors. By way of example, those PDE inhibitors may be mentioned such as are described and/or claimed in the following patent applications and patents: DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EPOl 12987, EPOl 16948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, U.S. Pat. Nos. 4,963,561, 5,141,931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517,

WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DEI 116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6,331,543, US20050004222 (including those disclosed in formulas I-XIII and paragraphs 37-39, 85-0545 and 557-577) and WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399.

PDE5 inhibitors which may be mentioned by way of example are RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra®). PDE4 inhibitors which may be mentioned by way of example are RO-20-1724, MEM 1414 (R1533/R1500; Pharmacia Roche), DENBUFYLLINE, ROLIPRAM, OXAGRELATE, NITRAQUAZONE, Y-590, DH-6471, SKF-94120, MOTAPIZONE, LIXAZINONE, INDOLIDAN, OLPRINONE, ATIZORAM, KS-506-G, DIPAMFYLLINE, BMY-43351, ATIZORAM, AROFYLLINE, FILAMINAST, PDB-093, UCB-29646, CDP-840, SKF- 107806, PICLAMILAST, RS- 17597, RS-25344-000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, MOPIDAMOL, ANAGRELIDE, IBUDILAST, AMRINONE, PIMOBENDAN, CILOSTAZOL, QUAZINONE and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide. PDE3 inhibitors which may be mentioned by way of example are SULMAZOLE, AMPIZONE, CILOSTAMIDE, CARBAZERAN, PIROXIMONE, IMAZODAN, CI-930, SIGUAZODAN, ADIBENDAN, SATERINONE, SKF-95654, SDZ-MKS-492, 349-U-85, EMORADAN, EMD-53998, EMD-57033, NSP-306, NSP-307, REVIZINONE, NM-702, WIN-62582 and WIN-63291, ENOXIMONE and MILRINONE. PDE3/4 inhibitors which may be mentioned by way of example are BENAFENTRINE, TREQUINSIN, ORG-30029, ZARDAVERINE, L-686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and TOLAFENTRINE. Other PDE inhibitors include: cilomilast, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®), zaprinast (PDE5 specific).

Anti- Uterine Contractions Agents

The GCRA peptides described herein can be used in combination therapy (for example, in order to decrease or inhibit uterine contractions) with a tocolytic agent including but not limited to beta-adrenergic agents, magnesium sulfate, prostaglandin inhibitors, and calcium channel blockers.

Anti- Neoplastic Agents

The GCRA peptides described herein can be used in combination therapy with an antineoplastic agents including but not limited to alkylating agents, epipodophyllotoxins, nitrosoureas, antimetabolites, vinca alkaloids, anthracycline antibiotics, nitrogen mustard agents, and the like. Particular anti-neoplastic agents may include tamoxifen, taxol, etoposide and 5-fluorouracil.

The GCRA peptides described herein can be used in combination therapy (for example as in a chemotherapeutic composition) with an antiviral and monoclonal antibody therapies.

Agents to treat Congestive Heart Failure

The GCRA peptides described herein can be used in combination therapy (for example, in prevention/treatment of congestive heart failure or another method described herein) with the partial agonist of the nociceptin receptor ORL1 described by Dooley et al. (The Journal of Pharmacology and Experimental Therapeutics, 283 (2): 735-741, 1997). The agonist is a hexapeptide having the amino acid sequence Ac- RYY (RK) (WI) (RK)-NH2 ("the Dooley polypeptide"), where the brackets show allowable variation of amino acid residue. Thus Dooley polypeptide can include but are not limited to KYYRWR, RYYRWR, KWRYYR, RYYRWK, RYYRWK (all-D amin acids), RYYRIK, RYYRIR, RYYKIK, RYYKIR, RYYKWR, RYYKWK, RYYRWR, RYYRWK, RYYRIK, RYYKWR, RYYKWK, RYYRWK and KYYRWK, wherein the amino acid residues are in the L-form unless otherwise specified. The GCRA peptides described herein can also be used in combination therapy with polypeptide conjugate modifications of the Dooley polypeptide described in WO0198324.

DOSAGE

Dosage levels of active ingredients in a pharmaceutical composition can also be varied so as to achieve a transient or sustained concentration of the compound in a subject, especially in and

around the site of inflammation or disease area, and to result in the desired response. It is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired effect and to gradually increase the dosage until the desired effect is achieved. It will be understood that the specific dose level for any particular subject will depend on a variety of factors, including body weight, general health, diet, natural history of disease, route and scheduling of administration, combination with one or more other drugs, and severity of disease.

An effective dosage of the composition will typically be between about 1 μg and about 10 mg per kilogram body weight, preferably between about 10 μg to 5 mg of the compound per kilogram body weight. Adjustments in dosage will be made using methods that are routine in the art and will be based upon the particular composition being used and clinical considerations.

The guanylate cyclase receptor agonists used in the methods described above may be administered orally, systemically or locally. Dosage forms include preparations for inhalation or injection, solutions, suspensions, emulsions, tablets, capsules, topical salves and lotions, transdermal compositions, other known peptide formulations and pegylated peptide analogs. Agonists may be administered as either the sole active agent or in combination with other drugs, *e.g.*, an inhibitor of cGMP-dependent phosphodiesterase and anti-inflammatory agent. In all cases, additional drugs should be administered at a dosage that is therapeutically effective using the existing art as a guide. Drugs may be administered in a single composition or sequentially.

Dosage levels of the GCR agonist for use in methods of this invention typically are from about 0.001 mg to about 10,000 mg daily, preferably from about 0.005 mg to about 1,000 mg daily. On the basis of mg/kg daily dose, either given in single or divided doses, dosages typically range from about 0.001/75 mg/kg to about 10,000/75 mg/kg, preferably from about 0.005/75 mg/kg to about 1,000/75 mg/kg.

The total daily dose of each inhibitor can be administered to the patient in a single dose, or in multiple subdoses. Typically, subdoses can be administered two to six times per day, preferably two to four times per day, and even more preferably two to three times per day. Doses can be in immediate release form or sustained release form sufficiently effective to obtain the desired control over the medical condition.

The dosage regimen to prevent, treat, give relief from, or ameliorate a medical condition or disorder, or to otherwise protect against or treat a medical condition with the combinations and compositions of the present invention is selected in accordance with a variety of factors.

These factors include, but are not limited to, the type, age, weight, sex, diet, and medical condition of the subject, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular inhibitors employed, whether a drug delivery system is utilized, and whether the inhibitors are administered with other active ingredients. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

EXAMPLES

EXAMPLE 1: SYNTHESIS AND PURIFICATION OF GCRA PEPTIDES

The GCRA peptides were synthesized using standard methods for solid-phase peptide synthesis. Either a Boc/Bzl or Fmoc/tBu protecting group strategy was seleceted depending upon the scale of the peptide to be produced. In the case of smaller quantities, it is possible to get the desired product using an Fmoc/tBu protocol, but for larger quantities (1 g or more), Boc/Bzl is superior.

In each case the GCRA peptide was started by either using a pre-loaded Wang (Fmoc) or Merrifield (Boc) or Pam (Boc) resin. For products with C-terminal Leu, Fmoc-Leu-Wang (D-1115) or Boc-Leu-Pam resin (D-1230) or Boc-Leu-Merrifield (D-1030) Thus, for peptides containing the C-terminal d-Leu, the resin was Fmoc-dLeu-Wang Resin (D-2535) and Boc-dLeu-Merrifield, Boc-dLeu-Pam-Resin (Bachem Product D-1230 and D-1590, respectively) (SP-332 and related analogs). For peptides produced as C-terminal amides, a resin with Ramage linker (Bachem Product D-2200) (Fmoc) or mBHA (Boc) (Bachem Product D-1210 was used and loaded with the C-terminal residue as the first synthetic step.

Fmoc-tBu Overview

Each synthetic cycle consisted deprotection with 20% piperidine in DMF. Resin washes were accomplished with alternating DMF and IpOH to swell and shrink the resin, respectively. Peptide synthesis elongated the chain from the C-terminus to the N-terminus. Activation chemistry for each amino acid was with HBTU/DIEA in a 4 fold excess for 45 minutes. In automated chemistries, each amino acid was double coupled to maximize the coupling efficiency. To insure the correct position of disulfide bonds, the Cys residues were introduced as Cys(Acm) at positions 15 and 7. Cys(Trt) was positioned at Cys4 and Cys12. This protecting

group strategy yields the correct topoisomer as the dominant product (75:25). (For enterotoxin analogs, a third disulfide bond protecting group (Mob) was utilized).

For peptides containing C-terminal Aeea (aminoethyloxyethyloxyacetyl) groups, these were coupled to a Ramage amide linker using the same activation chemistry above by using an Fmoc-protected Aeea derivative. The Cys numbering in these cases remains the same and the positioning of the protecting groups as well. For the peptides containing the N-terminal extension of Aeea, the Cys residue numbering will be increased by three Cys4 becomes Cys7, Cys12 becomes Cys15; Cys7 becomes Cys10 and Cys 15 becomes Cys18. The latter pair is protected with Acm and the former pair keeps the Trt groups.

For analogs containing D-amino acid substitutions, these were introduced directly by incorporating the correctly protected derivative at the desired position using the same activation chemistry described in this document. For Fmoc strategies, Fmoc-dAsn(Trt)-OH, Fmoc-dAsn(Xan)-OH, Fmoc-dAsp(tBu)-OH, Fmoc-dGlu(tBu)-OH and for Boc strategies, Boc-dAsn(Xan)-OH, Boc-dAsn(Trt)-OH, Boc-dAsp(Chx), Boc-dAsp(Bzl)-OH, Boc-dGlu(Chx)-OH and Boc-dGlu(Bzl)-OH would be utilized.

Each peptide is cleaved from the solid-phase support using a cleavage cocktail of TFA:H2O:Trisisopropylsilane (8.5:0.75:0.75) ml/g of resin for 2 hr at RT. The crude deprotected peptide is filtered to remove the spent resin beads and precipitated into ice-cold diethylether.

Each disulfide bonds was introduced orthogonally. Briefly, the crude synthetic product was dissolved in water containing NH_4OH to increase the pH to 9. Following complete solubilization of the product, the disulfide bond was made between the Trt deprotected Cys residues by titration with H_2O_2. The monocyclic product was purified by RP-HPLC. The purified mono-cyclic product was subsequently treated with a solution of iodine to simultaneously remove the Acm protecting groups and introduce the second disulfide bond.

For enterotoxin analogs, the Mob group was removed via treatment of the dicyclic product with TFA 85% containing 10% DMSO and 5% thioanisole for 2 hr at RT.

Each product was then purified by RP-HPLC using a combination buffer system of TEAP in H2O versus MeCN, followed by TFA in H2O versus MeCN. Highly pure fractions were combined and lyophilized. The final product was converted to an Acetate salt using either ion exchange with Acetate loaded Dow-Ex resin or using RP-HPLC using a base-wash step with NH_4OAc followed by 1% AcOH in water versus MeCN.

It is also possible to prepare enterotoxin analogs using a random oxidation methodology using Cys(Trt) in Fmoc or Cys(MeB) in Boc. Following cleavage, the disulfide bonds can be formed using disulfide interchange redox pairs such as glutathione (red/ox) and/or cysteine/cystine. This process will yield a folded product that the disulfide pairs must be determined as there would be no way of knowing their position directly.

Boc-Bzl Process

Peptide synthesis is initiated on a Merrifield or Pam pre-loaded resin or with mBHA for peptides produced as C-terminal amides. Each synthetic cycle consists of a deprotection step with 50% TFA in MeCL2. The resin is washed repetitively with MeCl2 and MeOH. The TFA salt formed is neutralized with a base wash of 10% TEA in MeCl2. The resin is washed with MeCl2 and MeOH and lastly with DMF prior to coupling steps. A colorimetric test is conducted to ensure deprotection. Each coupling is mediated with diisopropyl carbodiimide with HOBT to form the active ester. Each coupling is allowed to continue for 2 hr at RT or overnight on difficult couplings. Recouplings are conducted with either Uronium or Phosphonium reagents until a negative colorimetric test is obtained for free primary amines. The resin is then washed with DMF, MeCl2 and MeOH and prepared for the next solid-phase step. Cys protection utilizes Cys(Acm) at positions 7 and 15, and Cys(MeB) at Cys 4 and Cys12.

Cleavage and simultaneous deprotection is accomplished by treatment with HF using anisole as a scavenger (9:1:1) ml:ml:g (resin) at 0°C for 60 min. The peptide is subsequently extracted from the resin and precipitated in ice cold ether. The introduction of disulfide bonds and purification follows the exact same protocol described above for the *Fmoc-produced* product.

EXAMPLE 2: *IN VITRO* PROTEOLYTIC STABILITY USING SIMULATED GASTRIC FLUID (SGF) DIGESTION

The stability of SP-304 in the presence of simulated gastric fluid (SGF) was determined. SP-304 (final concentration of 8.5 mg/ml) was incubated in SGF (Proteose peptone (8.3 g/liter; Difco), D-Glucose (3.5 g/liter; Sigma), NaCl (2.05 g/liter; Sigma), KH_2PO_4 (0.6 g/liter; Sigma), $CaCl_2$ (0.11 g/liter), KCl (0.37 g/liter; Sigma), Porcine bile (final 1 X concentration 0.05 g/liter; Sigma) in PBS, Lysozyme (final 1 X concentration 0.10 g/liter; Sigma) in PBS, Pepsin (final 1 X concentration 0.0133 g/liter; Sigma) in PBS). SGF was made on the day of the experiment and

the pH was adjusted to 2.0 ± 0.1 using HCl or NaOH as necessary. After the pH adjustment, SGF is filter sterilized with 0.22 μm membrane filters. SP-304 (final concentration of 8.5 mg/ml) was incubated in SGF at 37°C for 0, 15, 30, 45, 60 and 120 min, respectively, in triplicate aliquots. Following incubations, samples were snap frozen in dry ice then stored in a -80°C freezer until assayed in duplicate.

Figure 1A is a bar chart showing the biological activity of SP-304 after incubation with SGF for times as indicated. The activity at 0 min was taken as 100%. The data are an average of triplicates ± SD for each data point. The data demonstrate that SP-304 is not sensitive to digestion with SGF. In addition, the data also suggest that the activity of SP-304 is not affected by exposure to the acidic pH of the SGF.

These results were further confirmed by the HPLC analyses of the samples after digestion with SGF. Here, aliquots of samples from all digestions were analyzed using a previously developed method for analyzing SP-304 peptide using HPLC. Samples from the SGF digestions were diluted to give a final concentration 0.17 mg/mL of SP-304. Figure 1B shows HPLC chromatographs of SP-304 samples after incubation with SGF at indicated times. The major peak of SP-304 did not change following digestion with SGF, indicating that the peptide was resistant to SGF digestion.

EXAMPLE 3: *IN VITRO* PROTEOLYTIC STABILITY USING SIMULATED INTESTINAL FLUID (SIF) DIGESTION

The stability of SP-304 was also evaluated after incubation with simulated intestinal fluid (SIF). SIF solution was prepared by the method as described in the United States Pharmacopoeia, 24th edition, p2236. The recipe to prepare SIF solution was as described below. The SIF solution contained NaCl (2.05 g/liter; Sigma), KH_2PO_4 (0.6 g/liter; Sigma), $CaCl_2$ (0.11 g/liter), KCl (0.37 g/liter; Sigma), and Pacreatin 10 mg/ml. The pH was adjusted to 6 and the solution was filter sterilized. A solution of SP-304 (8.5 mg/ml) was incubated in SGF at 37°C for 0, 30, 60, 90, 120, 150 and 300 min respectively, in triplicate aliquots. Following incubations, samples were removed and snap frozen with dry ice and stored in a -80°C freezer until assayed in duplicate. Figure 2A is a bar chart showing the ability of SP-304, after incubation in SIF for times as indicated, to stimulate cGMP synthesis in T84 cells. The cGMP stimulation activity at 0 min was taken as 100%. The data are an average of 3 triplicates ± SD.

The data indicated that the biological activity of SP-304 is reduced by 30% following digestion with SIF. This could be due to degradation of the peptide. Hence, samples after digestion with SIF were further analyzed by HPLC.

The integrity of SP-340 peptide exposed to SIF was evaluated by HPLC by essentially using the method described for SGF digestion. Figure 2B is a schematic representation of the results of HPLC chromatographic analyses of SP-304 samples after incubation with heat-inactivated SIF for 300 min, and SIF for 120 min, respectively. The major peak of SP-304, which elutes at 16.2 min was converted into another peak at 9.4 min and a few minor peptide peaks. Thus, it was important to find out structures of the metabolites of SP-304 produced after digestion with SIF. SP-304 peptide was incubated with SIF for various times and the peptide digestion products were isolated and subjected to structure elucidation by MS analysis.

Figure 3 is a schematic representation of the possible metabolites of SP-304. The major degradation products involve N and D clipped from the N-terminus and L from the C-terminus of SP304. However, there was only 30% reduction in biological activity, implying that one or more of the degradation products were also biologically active. To address this possibility, several truncated peptides were synthesized and evaluated for their abilities to stimulate cGMP synthesis in T84 cells (Figure 4).

Figure 4 shows data from the analyses of various peptides in the T84 cell cGMP stimulation assay (essentially as described in Shailubhai, *et al.*, Cancer Research 60, 5151-5157 (2000) . Briefly, confluent monolayers of T-84 cells in 24-well plates were washed twice with 250 µl of DMEM containing 50 mM HEPES (pH 7.4) and pre-incubated at 37°C for 10 minutes with 250 µl of DMEM containing 50 mM HEPES (pH 7.4) and 1 mM isobutyl methylxanthine (IBMX). Monolayers of T84 cells were then incubated with 250 µl of DMEM containing 50 mM HEPES (pH 7.4) containing one of the peptides shown in the Figure 4 at a concentration of 1.0 µM for 30 min. After the 30 min incubation, the medium was aspirated and the reaction was terminated by the addition of 3% perchloric acid. Following centrifugation and the addition of NaOH (0.1 N) to neutralize the pH, intracellular cGMP levels were determined in lysates using a cGMP ELISA kit (Cat. No. 581021 ; Cayman Chemical, Ann Arbor, MI). Samples were run in duplicates incubations and each sample was run as duplicates in ELISA test.

The data suggest that the leucine (L) residue at the C-terminus of SP-304 contributes to the biological potency of the peptide. For example, there was considerable reduction in potency when L was deleted from SP-304, as in SP-338. Similarly, the peptides SP-327, SP-329 and SP-331, without L at the C-terminal, also showed 20-25% reduction in biological potency as compared to their counterpart peptides with L at the C-terminus, as in SP-326, SP-328 and SP-330 peptides. In addition, results also suggest that amino acid residues at the N-terminus might also be important for stability and/or potency of the peptides. Based on these results, several new peptides were synthesized with D-forms of amino acids replacing the corresponding L-forms at the C- and N-termini of the peptides. These peptides were evaluated for their abilities to stimulate cGMP synthesis in T84 cells as shown in Figure 5.

The results presented in Figure 5 suggest that substitution of L-amino acids with D-amino acids at the C- and N-termini did not significantly alter their potency. Peptides SP-332, SP-333 and SP-335 showed comparable ability to stimulate cGMP synthesis in T84 cells. On the other hand, the substitution of L-leucine with D-leucine at the 6^{th} position in SP-337 resulted in a complete loss in its ability to stimulate cGMP synthesis in T84 cells. These results suggest that the amino acid residues Asn, Asp and Glu at the N-terminus and Leu at the C-terminus can be replaced with their respective D- amino acid forms. However, the leucine at the 6^{th} position can not be replaced with its D-form.

Figure 7 (A-F) shows the stabilities of peptides SP-332, SP-333 and SP-304 when incubated with SIF for two hours. The results demonstrated that the peptide SP-333, which has D-Asn at the N-terminus and D-Leu at the C-terminus, was virtually completely resistant to digestion with SIF (Figure 7F), and remained virtually 100% biologically active after a two hour incubation in SIF (Figure 7A). The peptide SP-332 with D-Leu at the C-terminus showed some reduction in potency following the 120 min incubation with SIF (Figure 7B). However, the HPLC analyses of SP-332 did not reveal any degradation of the peptide (Figure 7E), suggesting that these peptides are completely resistant to proteoysis by SIF. On the other hand, the peptide SP-304 lost about 30% of its potency following digestion with SIF for just one hour (Figure 7C). The HPLC analysis of SP-304 following SIF incubation confirmed its degradation (Figure 7D). These results suggest that the peptide SP-304 undergoes proteolysis following incubation with SIF, whereas substitution of L-Asn with D-Asn at the N-terminus plus the substitution of L-Leu

with D-Leu at the C-terminus protects SP-333 against digestion with SIF. Thus, the peptide SP-333 appears more stable and potent as a drug candidate.

EXAMPLE 4: CYCLIC cGMP STIMULATION ASSAYS

The ability of the GCRA peptide to bind to and activate the intestinal GC-C receptor was tested by usingT 84 human colon carcinoma cell line. Human T84 colon carcinoma cells were obtained from the American Type Culture Collection. Cells were grown in a 1:1 mixture of Ham's F-12 medium and Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 100 U penicillin/ml, and 100 μg/ml streptomycin. The cells were fed fresh medium every third day and split at a confluence of approximately 80%.

Biological activity of the GCRA peptides was assayed as previously reported (Shailubhai, *et al.*, Cancer Research 60, 5151-5157 (2000)). Briefly, the confluent monolayers of T-84 cells in 24-well plates were washed twice with 250 μl of DMEM containing 50 mM HEPES (pH 7.4), pre-incubated at 37°C for 10 min with 250 μl of DMEM containing 50 mM HEPES (pH 7.4) and 1 mM isobutylmethylxanthine (IBMX), followed by incubation with GCRA peptides (0.1 nM to 10 .mu.M) for 30 min. The medium was aspirated, and the reaction was terminated by the addition of 3% perchloric acid. Following centrifugation, and neutralization with 0.1 N NaOH, the supernatant was used directly for measurements of cGMP using an ELISA kit (Caymen Chemical, Ann Arbor, Mich.).

Figure 6 shows results from the experiments evaluating potency of peptides that are similar to the *E. coli* enterotoxin ST peptide in the cGMP stimulation assay (as above). Among these the peptides SP-353 and SP-354 were found to be quite potent to stimulate cGMP synthesis in T84 cells. Particularly, the peptide SP-353 that has Ser residue at the 6^{th} position was found to be the most potent among the peptides tested. The peptide SP-355 that has D-Tyr at the C-terminus showed potency markedly less than the other peptides.

EXAMPLE 5: PEGGYLATED PEPTIDES

An additional strategy to render peptides more resistant towards digestion by digestive proteases is to peggylate them at the N- and C-terminus. The peptide SP-333 was peggylated with the aminoethyloxy-ethyloxy-acetic acid (Aeea) group at the C-terminus (SP-347) or at the N-terminus (SP-350) or at both termini (SP-343). Cyclic GMP synthesis in T84 cells was measured by the method as described above.

The peptides SP-347 and SP-350 showed potencies comparable to SP-333 in their abilities to stimulate cGMP synthesis in T84 cells. However, peptide SP-343 was considerably less potent as compared to the other peptides tested. The poor activity of SP-343 might be due to the considerable steric hindrance afforded by the large Aeea groups at both termini.

EXAMPLE 6: COMBINATION OF GUANYLATE CYCLASE AGONISTS WITH PHOSPHODIESTERASE INHIBITORS

Regulation of intracellular concentrations of cyclic nucleotides (*i.e.*, cAMP and cGMP) and thus, signaling via these second messengers, has been generally considered to be governed by their rates of production versus their rates of destruction within cells. Thus, levels of cGMP in tissues and organs can also be regulated by the levels of expression of cGMP-specific phosphodiesterases (cGMP-PDE), which are generally overexpressed in cancer and inflammatory diseases. Therefore, a combination consisting of an agonist of GC-C with an inhibitor of cGMP-PDE might produce synergistic effect on levels of cGMP in the target tissues and organs.

Sulindac Sulfone (SS) and Zaprinast (ZAP) are two of the known inhibitors of cGMP-PDE and have been shown to induce apoptosis in cancer cells via a cGMP-dependent mechanism. SS and ZAP in combination with SP304 or SP-333 was evaluated to see if these PDE inhibitors had any synergistic effect on intracellular accumulation of cGMP (Fig. 9-12). As the data shows, SS at concentration of 100 μM did not enhance intracellular accumulation of cGMP. However, the combination SS with SP304 stimulated cGMP production several fold more then the stimulation by SP304 used alone. This synergistic effect on cGMP levels was more pronounced when SP304 were used at 0.1 μM concentration (Fig 10). Similar observations were made when SP304 or SP333 were used in combination with ZAP (Fig 10, Fig 11 and Fig 12). These results suggest that the intracellular levels of cGMP are stabilized because SS inhibits cGMP-PDE that might be responsible for depletion of intracellular cGMP. Thus, the approach to use a combination of GC-C agonist with a cGMP-PDE inhibitor is attractive.

For the results shown in Figure 9, cyclic GMP synthesis in T84 cells was assessed essentially as described in Shailubhai et al., Cancer Research 60, 5151-5157 (2000). Briefly, confluent monolayers of T-84 cells in 24-well plates were washed twice with 250 μl of DMEM containing 50 mM HEPES (pH 7.4) and pre-incubated at 37°C for 10 minutes with 250 μl of DMEM containing 50 mM HEPES (pH 7.4) and 1 mM isobutyl methylxanthine (IBMX).

Monolayers of T84 cells were then incubated with 250 µl of DMEM containing 50 mM HEPES (pH 7.4) containing SP-304 or PDE inhibitors either alone or in combinations, as indicated below in the following experimental sets: 1) Control; 2) SP-304 (0.1 µM); 3) Sulindac Sulfone (100 µM); 4) Zaprinast (100 µM); 5) SP-304 (0.1 µM) + Sulindac Sulfone (100 µM); and 6) SP-304 (0.1 µM) + Zaprinast (100 µM). After the 30 min incubation, the medium was aspirated and the reaction was terminated by the addition of 3% perchloric acid. Following centrifugation and the addition of NaOH (0.1 N) to neutralize the pH, intracellular cGMP levels were determined in lysates using a cGMP ELISA kit (Cat. No. 581021 ; Cayman Chemical, Ann Arbor, MI). Samples were run in duplicates incubations and each sample was run as duplicates in ELISA test.

For the results shown in Figure 10, the method used was same as the one used for Fig. 9 except that the monolayers of T84 cells were incubated with 500 µl of DMEM containing 50 mM HEPES (pH 7.4) containing SP-304 (0.1 or 1.0 µM) or increasing concentrations of PDE inhibitors (0 to 750 µM) either alone or in combination with SP-304. After the 30 min incubation, the medium was aspirated and the reaction was terminated by the addition of 3% perchloric acid. Following centrifugation and the addition of NaOH (0.1 N) to neutralize the pH, intracellular cGMP levels were determined in lysates using a cGMP ELISA kit (Cat. No. 581021; Cayman Chemical, Ann Arbor, MI). Samples were run as triplicates in ELISA test.

For the results shown in Figure 11, the method used was same as the one used for Fig. 10 except that the monolayers of T84 cells were incubated with 500 µl of DMEM containing 50 mM HEPES (pH 7.4) containing SP-3333 (0.1 or 1.0 µM) or increasing concentrations of ZAP (0 to 500 µM) either alone or in combination with SP-333. After the 30 min incubation, the medium was aspirated and the reaction was terminated by the addition of 3% perchloric acid. Following centrifugation and the addition of NaOH (0.1 N) to neutralize the pH, intracellular cGMP levels were determined in lysates using a cGMP ELISA kit (Cat. No. 581021 ; Cayman Chemical, Ann Arbor, MI). Samples were run as triplicates in ELISA test.

For the results shown in Figure 12, the method used was same as the one used for Fig. 10 except that the monolayers of T84 cells were incubated with 500 µl of DMEM containing 50 mM HEPES (pH 7.4) containing SP-333 (0.1 µM) or increasing concentrations of Sulindac Sulfone (0 to 500 µM) either alone or in combination with SP-333. After the 30 min incubation, the medium was aspirated and the reaction was terminated by the addition of 3% perchloric acid.

Following centrifugation and the addition of NaOH (0.1 N) to neutralize the pH, intracellular cGMP levels were determined in lysates using a cGMP ELISA kit (Cat. No. 581021 ; Cayman Chemical, Ann Arbor, MI). Samples were run as triplicates using the ELISA test.

EXAMPLE 7: AN ORAL RANGE-FINDING TOXICITY STUDY IN CYNOMOLGUS MONKEYS.

The objective of the study is to determine the toxicity of the GRCA peptides according to the invention following a single oral gavage administration to the cynomolgus monkey and to allow assessment of reversibility of any changes following a minimum 7-day observation/washout period. Each GRCA peptide according to the invention will be given at two different dose levels.

Experimental Design

The test (e.g., the GRCA peptides according to the invention) and control/vehicle article will be administered in three phases separated by a minimum 7-day observation period. Each phase will consist of a single oral gavage administration to female cynomolgus monkeys as indicated in the tables below:

Phase 1:

Eight non-naive female cynomolgus monkeys will be transferred from the ITR Spare Monkey colony and assigned to four dose groups as follows:

Group Number	Group Designation	Study Days	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals (Females)
1	Control/Vehicle	1	0	0	10	2
		4				
2	Test Peptides	1	1	0.1	10	2
		4				
		4				

Following completion of the Phase 1 dosing, all monkeys will be observed for 33 days. Upon completion of the observation period, all monkeys will be transferred back to the ITR Spare Monkey Colony.

Phase 2:

The same eight non-naïve female cynomolgus monkeys as previously used in Phase 1 will be transferred from the ITR Spare Monkey colony and assigned to four dose groups as follows:

Group Number	Group Designation	Study Day	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals (Females)
1	Control/Vehicle	1	10	1	10	2
2	Test Peptides	1	10	1	10	2

Following completion of the Phase 2 dosing, all monkeys will be observed for a minimum of 7 days.

Route of Administration

The oral route of administration has been chosen because it is a preferred human therapeutic route.

Preparation of Test and Control /Vehicle Articles

The test and control/vehicle articles will be prepared fresh on the day of dosing in cold distilled water (maintained in an ice water bath). A sufficient amount of test article powder will be added to the appropriate amount of distilled water in order to achieve the desired concentration. The dose formulations will be mixed by simple inversion.

Analysis of Test Article Concentration and Stability in the Dose Formulations

For possible confirmation of the concentration and stability of the test article in the formulations, representative samples will be taken from the middle of each concentration, including the control/vehicle article on the first day of dosing of each group, as indicated below. Samples will be collected immediately after preparation on Day 1 and again after dosing is completed on that day and will be stored frozen (approximately 80°C nominal) in 20 mL screw cap vials. Therefore, the remaining dose formulation vials will be returned to the Pharmacy Department as soon as possible after completion of dosing.

Group 1: 1.5 mL in duplicate from the middle on Day 1 (pre-dose and post-dose).

Group 2: 1.5 mL in duplicate from the middle on Day 1 (pre-dose and post-dose).

Group 3: 1.5 mL in duplicate from the middle on Day 1 (pre-dose and post-dose).

Group 4: 1.5 mL in duplicate from the middle on Day 1 (pre-dose and post-dose).

The formulations will be maintained cold in an ice water bath during all sampling procedures.

The formulations will be stirred continuously with a stir bar for a minimum of 15 minutes prior to sampling.

The samples will be retained frozen (approximately -80°C nominal) at ITR until requested by the Sponsor to be shipped to a laboratory designated by the Sponsor for analysis. The samples can be discarded once it is determined by the analyst and Study Director that they are no longer needed. These samples' disposition will be recorded in the raw data.

If analyzed, a Dose Formulation report will be prepared by the Principal Investigator (Formulation analysis) and will be provided to ITR for inclusion in the final report.

Test System

Species/Strain:	Cynomolgus Monkey *(Macaca Fasicularis)*
Source:	orldwide Primates Inc., P.O. Box 971279 Miami, Florida, 33187, USA *and* Covance Research Products Inc. P.O. Box 549 Alice, Texas, 78333, USA
Total No. of monkeys on study:	8 non-naive females
Body Weight Range:	2-4 kg at onset of treatment
Age Range at Start:	Young adult at onset of treatment
Acclimation Period:	The animals will be transferred from ITR's spare monkey colony. They are therefore, considered to be fully acclimated to the laboratory environment.

The actual age and body weight ranges will be noted in the final report.

Administration of the Test and Control/Vehicle Articles

The test and control/vehicle articles will be administered by oral gavage administration using a gavage tube attached to a syringe in three Phases separated by a minimum 7-day

observation/washout period. Each dosing session will consist of a single oral gavage administration. The gavage tube will be flushed with 3 mL of reverse osmosis water immediately following administration of the dose formulation in order to ensure that the entire dose volume has been delivered to the animal. The dose volume will be 10 mL/kg for all animals, including controls. The actual volume administered to each monkey on Day 1 of each Phase will be calculated using the Day -1 body weights of each Phase.

Dosing formulations will be maintained cold during dose administration by placing them in an ice water bath.

The dosing formulations must be placed on a stir plate for a minimum of 15 minutes prior to the start of dosing and maintained on the stir plate throughout the dosing procedure.

The dosing formulations must be used within 2 hours of preparation.

Clinical Observations

Cage-side clinical signs (ill health, behavioral changes etc.) will be recorded as indicated below except on detailed clinical examination days, where the morning cage-side clinical signs will be replaced by a detailed clinical examination (DCE). During regular cage side clinical signs and detailed examinations, particular attention will be paid to stools with respect to amount of stools produced, description of stools, etc.

Cage side clinical signs will be performed as follows:

During the pretreatment period and during the 7-day (minimum) observation periods: Three times per day with a minimum of 3 hours between each occasion.

On the dosing day of Phase 1: pre-dose, 2, 4, 6, 8 and 24 hours post-dosing

On the dosing day of Phase 2: pre-dose, continuously for the first 4 hours post-dose and at 6, 8 and 24 hours post-dosing

On the dosing day of Phase 3: pre-dose, continuously for the first 4 hours post-dose and at 6, 8 and 24 hours post-dosing

A detailed clinical examination of each monkey will be performed once at the time of animal transfer and once weekly thereafter.

Animals whose health status is judged to warrant additional evaluation will be examined by a Clinical Veterinarian, or a technician working under the supervision of the Clinical Veterinarian. Any veterinarian-recommended treatments will only be performed once agreement has been obtained from the Study Director. Where possible, the Sponsor will be consulted prior to administration of therapeutic drugs.

Body weights will be recorded for all animals once daily from the day of transfer through to the end of the study.

Food consumption will be recorded for all animals once daily from the day of transfer through to the end of the study.

Cages will be cleaned prior to the start of the daily food consumption to ensure no food cookies remain in the cage. Monkeys will be fed 7 cookies before 12pm and 7 cookies after 12pm. The sum of the total number of cookies given for the day will be recorded.

The next morning, a visual check will be performed to see how many cookies are left in the cage. The number of whole cookies remaining in the food hopper or on the tray will be recorded. The number of whole cookies left will be subtracted from the total number of cookies given in order to calculate the number of cookies eaten.

EXAMPLE 8: SUCKLING MOUSE MODEL OF INTESTINAL SECRETION (SUMI ASSAY)

The GCRA peptides described herein can be tested for their ability to increase intestinal secretion using a suckling mouse model of intestinal secretion. In this model a GCRA peptide is administered to suckling mice that are between seven and nine days old. After the mice are sacrificed, the gastrointestinal tract from the stomach to the cecum is dissected ("guts"). The remains ("carcass") as well as the guts are weighed and the ratio of guts to carcass weight is calculated. If the ratio is above 0.09, one can conclude that the test compound increases intestinal secretion. Controls for this assay may include wild-type SP-304, ST polypeptide and Zelnorm®.

Phenylbenzoquinone-induced writhing model

The PBQ-induced writhing model can be used to assess pain control activity of the GCRA peptide described herein. This model is described by Siegmund et al. (1957 Proc. Soc. Exp. Bio. Med. 95:729-731). Briefly, one hour after oral dosing with a test compound, e.g., a GCRA peptide, morphine or vehicle, 0.02% phenylbenzoquinone (PBQ) solution (12.5 mL/kg)

is injected by intraperitoneal route into the mouse. The number of stretches and writhings are recorded from the 5th to the 10th minute after PBQ injection, and can also be counted between the 35th and 40th minute and between the 60th and 65th minute to provide a kinetic assessment. The results are expressed as the number of stretches and writhings (mean ± SEM) and the percentage of variation of the nociceptive threshold calculated from the mean value of the vehicle-treated group. The statistical significance of any differences between the treated groups and the control group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software.

EXAMPLE 9 : PHARMACOKINETIC PROPERTY DETERMINATION OF GCRA PEPTIDES

Serum samples are extracted from the whole blood of exposed (mice dosed orally or intravenously with GCRA peptides (s) described herein) and control mice, then injected directly (10 mL) onto an in-line solid phase extraction (SPE) column (Waters Oasis HLB 25μm column, 2.0 x 15mm direct connect) without further processing. The sample on the SPE column is washed with a 5% methanol, 95% dH_2O solution (2.1 mL/min, 1.0 minute), then loaded onto an 0 analytical column using a valve switch that places the SPE column in an inverted flow path onto the analytical column (Waters Xterra MS C8 5μm IS column, 2.1 x 20mm). The sample is eluted from the analytical column with a reverse phase gradient (Mobile Phase A: 10 mM ammonium hydroxide in dH_2O, Mobile Phase B: 10 mM ammonium hydroxide in 80% acetonitrile and 20% methanol; 20% B for the first 3 minutes then ramping to 95% B over 4 min. and holding for 2 5 min., all at a flow rate of 0.4 mL/min.). At 9.1 minutes, the gradient returns to the initial conditions of 20%B for 1 min. polypeptide is eluted from the analytical column and is detected by triple-quadrapole mass spectrometry (MRM, 764 (+2 charge state)>182 (+1 charge state) Da; cone voltage = 30V; collision = 20 eV; parent resolution = 2 Da at base peak; daughter resolution = 2 Da at base peak). Instrument response is converted into concentration units by comparison with a standard curve using known amounts of chemically synthesized polypeptide(s) prepared and injected in mouse plasma using the same procedure.

Similarly, pharmacokinetic properties are determined in rats using LCMS methodology. Rat plasma samples containing the GCRA peptide are extracted using a Waters Oasis MAX 96 well solid phase extraction (SPE) plate. A 200 μL volume of rat plasma is mixed with 200 μL of ^{13}Cg, ^{15}N -labeled polypeptide in the well of a prepared SPE plate. The samples are drawn

through the stationary phase with 15 mm Hg vacuum. All samples are rinsed with 200 μL of 2% ammonium hydroxide in water followed by 200 μL of 20% methanol in water. The samples are eluted with consecutive 100 μL volumes of 5/20/75 formic acid/water/methanol and 100 μL 5/15/80 formic acid/water/methanol. The samples are dried under nitrogen and resuspended in 100 μL of 20% methanol in water. Samples are analyzed by a Waters Quattro Micro mass spectrometer coupled to a Waters 1525 binary pump with a Waters 2777 autosampler. A 40 μL volume of each sample is injected onto a Thermo Hypersil GOLD C18 column (2.1x50 mm, 5 um). polypeptide is eluted by a gradient over 3 minutes with acetonitrile and water containing 0.05% trifluoroacetic acid. The Quattro Micro mass spectrometer is run in multiple reaction monitoring (MRM) mode using the mass transitions of, for example 764>182 or 682>136. Using this methodology, polypeptide is dosed orally and by IV to rats at 10 mg/kg. Pharmacokinetic properties including area under the curve and bioavailabilty are determined.

EXAMPLE 10: DIURESIS RELATED EXPERIMENTS EFFECT ON DIURESIS AND NATRIURESIS

The effect of GCRA peptides described herein on diuresis and natriuresis can be determined using methodology similar to that described in WO06/001931 (examples 6 (p. 42) and 8 (p.45)). Briefly, the polypeptide/agonist described herein (180-pmol) is infused for 60 min into a group of 5 anesthetized mice or primates. Given an estimated rat plasma volume of 10 mL, the infusion rate is approximately 3 pmol/mL/min. Blood pressure, urine production, and sodium excretion are monitored for approximately 40 minutes prior to the infusion, during the infusion, and for approximately 50 minutes after the infusion to measure the effect of the GCRA peptides on diuresis and natriuresis. For comparison, a control group of five rats is infused with regular saline. Urine and sodium excretion can be assessed. Dose response can also be determined. polypeptide/GC-C agonist described herein is infused intravenously into mice or primates over 60 minutes. Urine is collected at 30 minute intervals up to 180 minutes after termination of polypeptide/GC-C agonist infusion, and urine volume, sodium excretion, and potassium excretion are determined for each collection interval. Blood pressure is monitored continuously. For each dose a dose-response relationship for urine volume, sodium and potassium excretion can be determined. Plasma concentration of the polypeptide/GC-agonist is also determined before and after iv infusion.

Mouse or Primate Diuresis Experiment: Once an appropriate level of anesthesia has been achieved, a sterile polyurethane catheter is inserted into the urethra and secured using 1 - 2 drops of veterinary bond adhesive applied to urethra/catheter junction. Animals are then dosed with either vehicle or test article via the intravenous or intraperitoneal route. Animals are allowed to regain consciousness, and the volume of urine excreted over a 1-5 hour duration is recorded periodically for each rat.

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We claim:

1. A peptide consisting essentially of the amino acid sequence of any one of SEQ ID NO:2-54 and 57-98.

2. A pharmaceutical composition in unit dose comprising a guanylate cyclase receptor agonist peptide having the sequence of any one of NO:2-54 and 56-94 present in a therapeutically effective amount and a pharmacetical carrier, excipient or diluent.

3. The peptide of claim 1, wherein said peptide is SEQ ID NO: 8, 9, 10, 58 or 59.

4. The pharmaceutical composition of claim 2, wherein said peptide is SEQ ID NO: 8, 9, 10, 58 or 59.

5. The peptide of claim 1, wherein said peptide is SEQ ID NO: 45-54 and said peptide increases cGMP production in a cell and wherein said peptide is not SEQ ID NO:1.

6. The pharmaceutical composition of claim 2, wherein said peptide is SEQ ID NO: 45-54, and said peptide increases cGMP production in a cell and wherein said peptide is not SEQ ID NO:1.

7. The peptide of claim 1, wherein said peptide is SEQ ID NO: 87-98, and said peptide increases cGMP production in a cell and wherein said peptide is not SEQ ID NO:55 or 56.

8. The pharmaceutical composition of claim 2, wherein said peptide is SEQ ID NO: 87-98, and said peptide increases cGMP production in a cell and wherein said peptide is not SEQ ID NO:55 or 56.

9. The pharmaceutical composition of any one of claims claim 2, 4, 6, or 8, wherein the unit dose form is selected from the group consisting of a tablet, a capsule, a solution or inhalation formulation.

10. A method for preventing or treating a condition selected from the group consisting of Ulcerative Colitis, Irritable bowel syndrome (IBS), non-ulcer dyspepsia chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, constipation associated with use of opiate pain killers, gastroesophageal reflux disease (GERD), post surgical constipation, gastroparesis, constipation associated with neuropathic disorders, heartburn, poor gastrointestinal motility , congestive heart failure, hypertension, benign prostatic hyperplasia (BPH), colon cancer, lung cancer, bladder cancer, liver cancer,

salivary gland cancer or skin cancer, bronchitis, tissue inflammation, organ inflammation, respiratory inflammation, asthma, COPD comprising administering toa patient in need thereof, an effective dosage of a guanylate cyclase receptor agonist having the sequence of any one of NO:2-54 and 56-94.

11. The method of claim 10, wherein said peptide is SEQ ID NO: 8, 9, 10, 58 or 59.

12. A method of claim 11 or 12, further comprising administering an effective dose of inhibitor of a cGMP-specific phosphodiesterase.

13. The method of claim 12, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

14. The method of claim 12, wherein said cGMP-dependent phosphodiesterase inhibitor is selected from the group consisting of suldinac sulfone, zaprinast, and motapizone, vardenifil, and suldenifil.

15. The method of claim 12, futher comprising administering an effective does of at least one anti-inflammatory agent.

16. The method of claim12, wherein an anti-inflammatory agent is a steroid or nonsteroid anti-inflammatory drug (NISAIDS).

17 The use of any one of the peptides having the sequence of any one of SEQ ID NO:2-54 and 56-94 in the manufacture of a medicament for the treatment of a human disease.

18. The useof claim 17, wherein said peptide is SEQ ID NO: 8, 9, 10, 58 or 59.

19. A method of increasing cGMP production in a cell comprising contacting said cell with a peptide selected from the group consisting of the amino acid sequence of SEQ ID NO:2-54 and 57-98.

20. The method of claim 19, further comprising contacting said cell with a phosphodiesterase inhibitor.

21. The method of claim 20, wherein said cGMP-dependent phosphodiesterase inhibitor is selected from the group consisting of suldinac sulfone, zaprinast, and motapizone, vardenifil, and suldenifil.

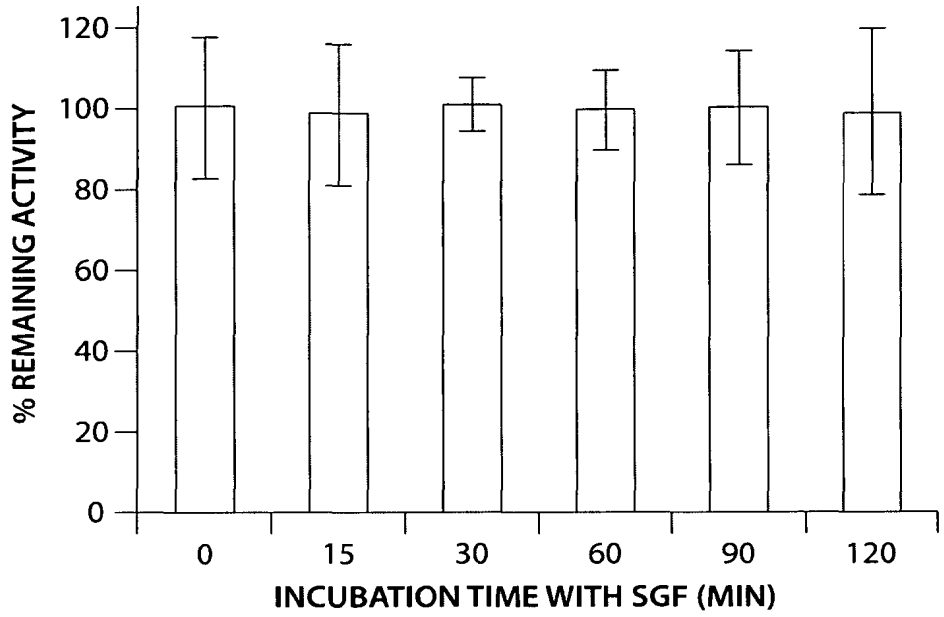

120
100
80
60
40
20
0
% REMAINING ACTIVITY
0
15
30
60
90
120
INCUBATION TIME WITH SGF (MIN)

Fig. 1A

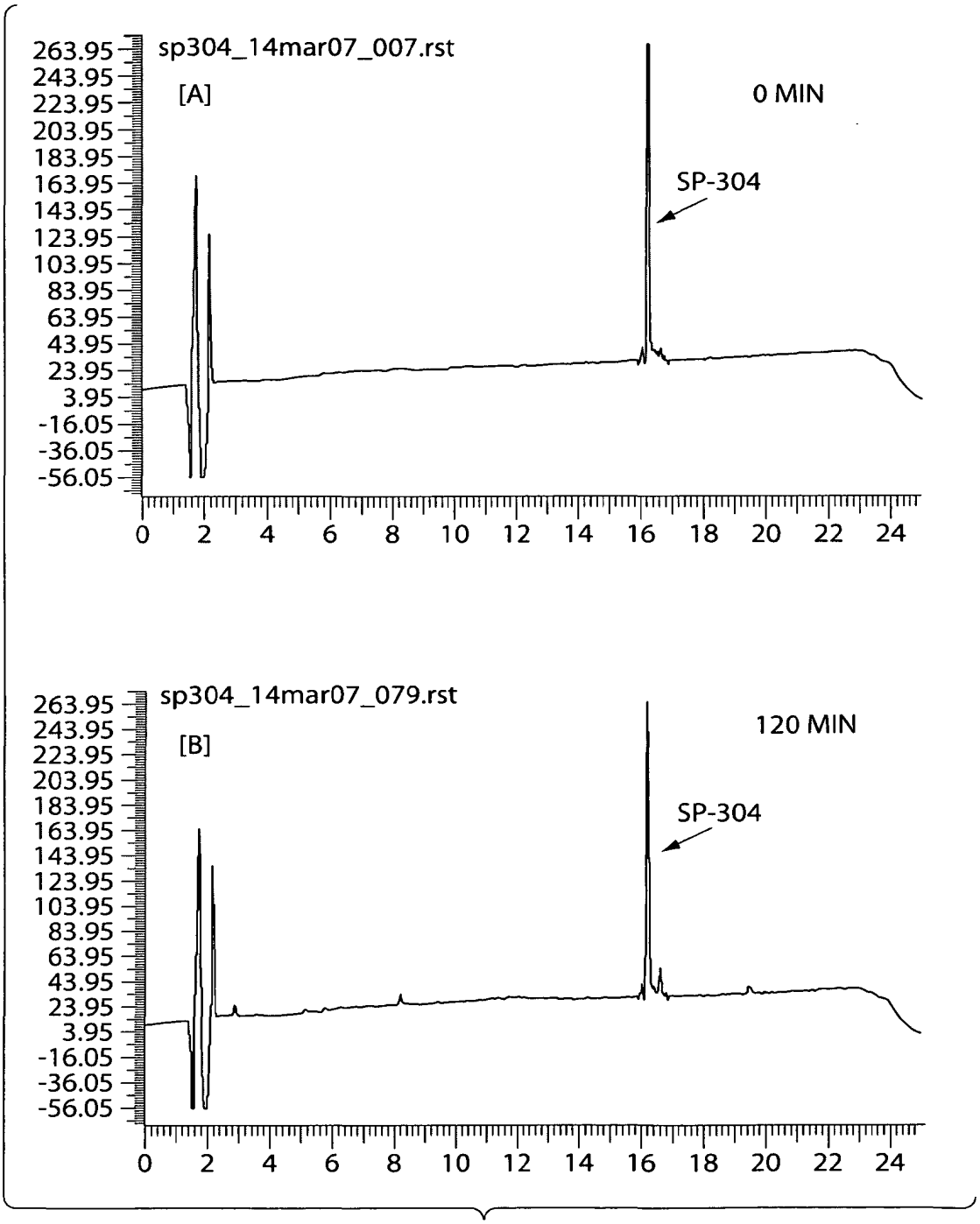

sp304_14mar07_007.rst
[A]
0 MIN
SP-304
263.95
243.95
223.95
203.95
183.95
163.95
143.95
123.95
103.95
83.95
63.95
43.95
23.95
3.95
-16.05
-36.05
-56.05
0 2 4 6 8 10 12 14 16 18 20 22 24
sp304_14mar07_079.rst
[B]
120 MIN
SP-304
263.95
243.95
223.95
203.95
183.95
163.95
143.95
123.95
103.95
83.95
63.95
43.95
23.95
3.95
-16.05
-36.05
-56.05
0 2 4 6 8 10 12 14 16 18 20 22 24

Fig. 1B

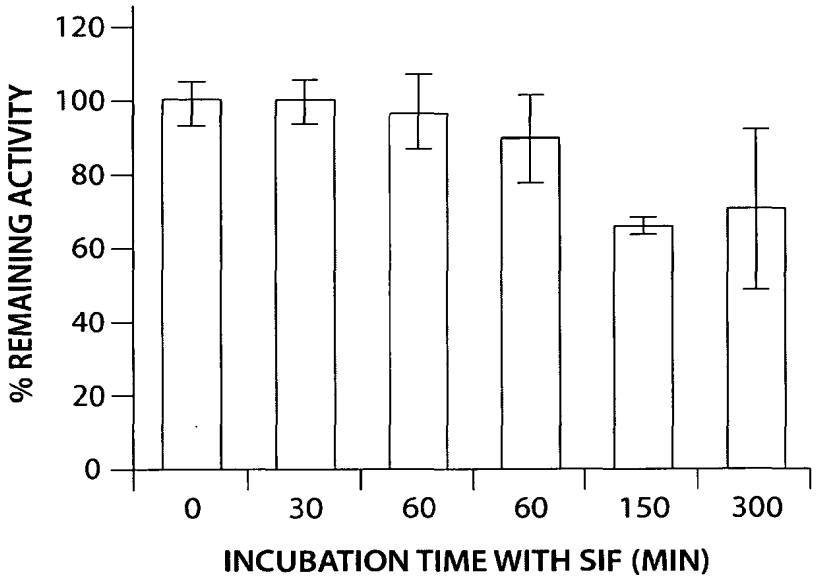
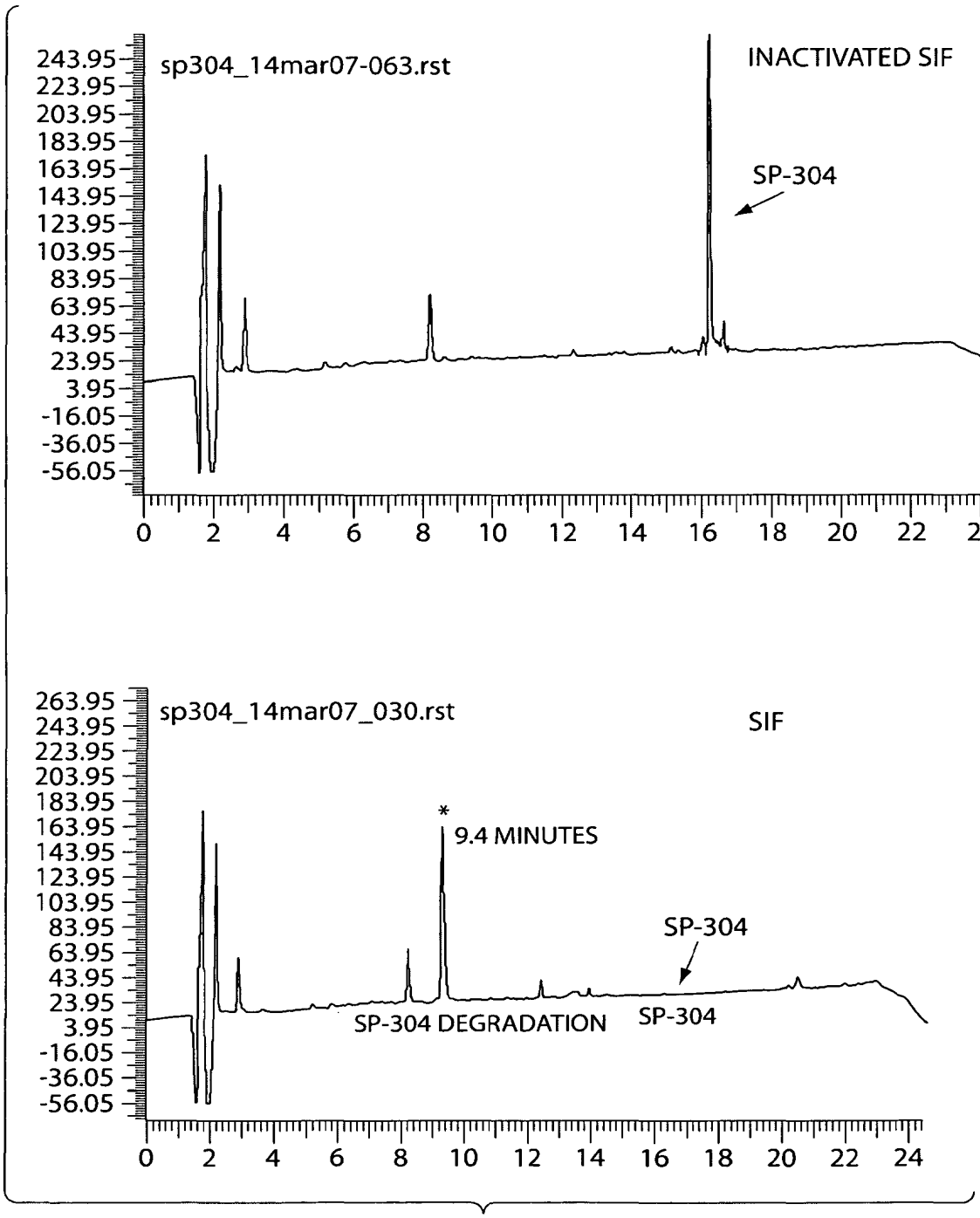

120
100
80
60
40
20
0
% REMAINING ACTIVITY
0
30
60
60
150
300
INCUBATION TIME WITH SIF (MIN)

Fig. 2A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INACTIVATED SIF
SP-304
243.95
223.95
203.95
183.95
163.95
143.95
123.95
103.95
83.95
63.95
43.95
23.95
3.95
-16.05
-36.05
-56.05
0 2 4 6 8 10 12 14 16 18 20 22 24
sp304_14mar07_030.rst
SIF
*
9.4 MINUTES
SP-304
SP-304 DEGRADATION
SP-304
263.95
243.95
223.95
203.95
183.95
163.95
143.95
123.95
103.95
83.95
63.95
43.95
23.95
3.95
-16.05
-36.05
-56.05
0 2 4 6 8 10 12 14 16 18 20 22 24

Fig. 2B

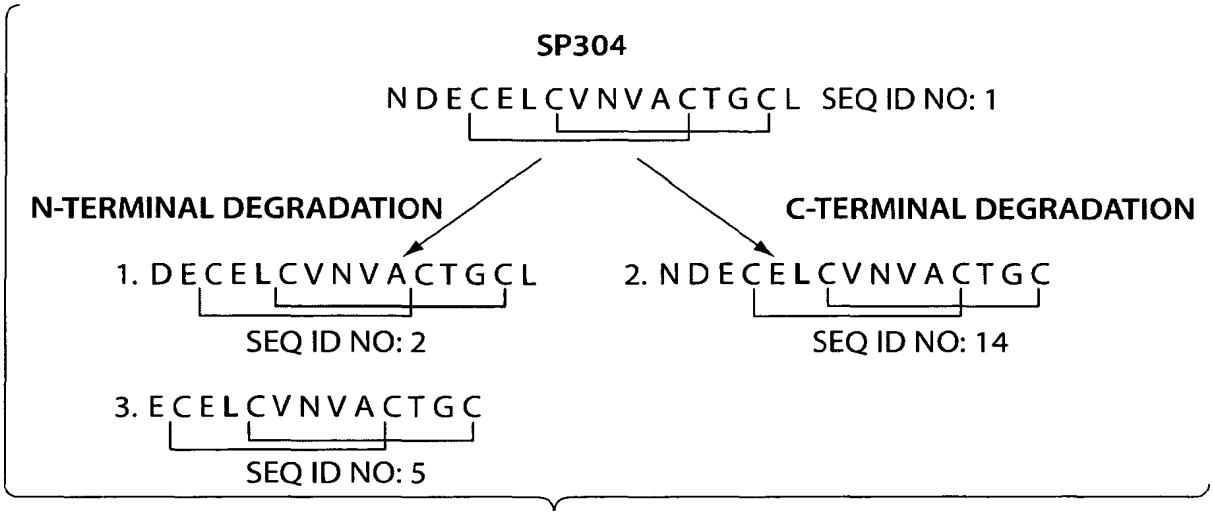
SP304
N D E C E L C V N V A C T G C L SEQ ID NO: 1
N-TERMINAL DEGRADATION
C-TERMINAL DEGRADATION
1. D E C E L C V N V A C T G C L
SEQ ID NO: 2
2. N D E C E L C V N V A C T G C
SEQ ID NO: 14
3. E C E L C V N V A C T G C
SEQ ID NO: 5

Fig. 3

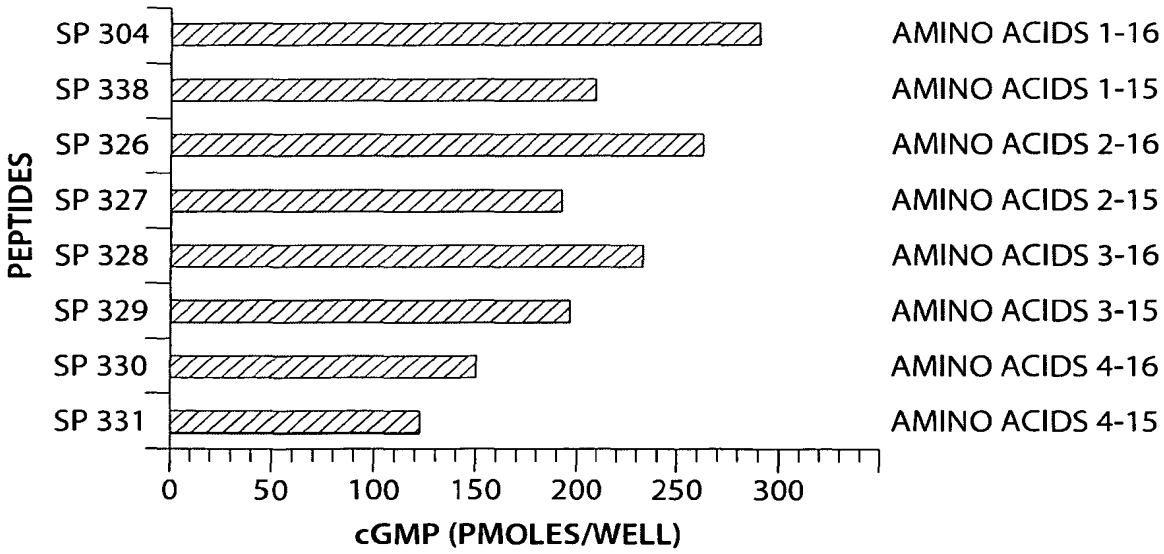
SP 304
SP 338
SP 326
SP 327
SP 328
SP 329
SP 330
SP 331
PEPTIDES
AMINO ACIDS 1-16
AMINO ACIDS 1-15
AMINO ACIDS 2-16
AMINO ACIDS 2-15
AMINO ACIDS 3-16
AMINO ACIDS 3-15
AMINO ACIDS 4-16
AMINO ACIDS 4-15
0
50
100
150
200
250
300
cGMP (PMOLES/WELL)

Fig. 4

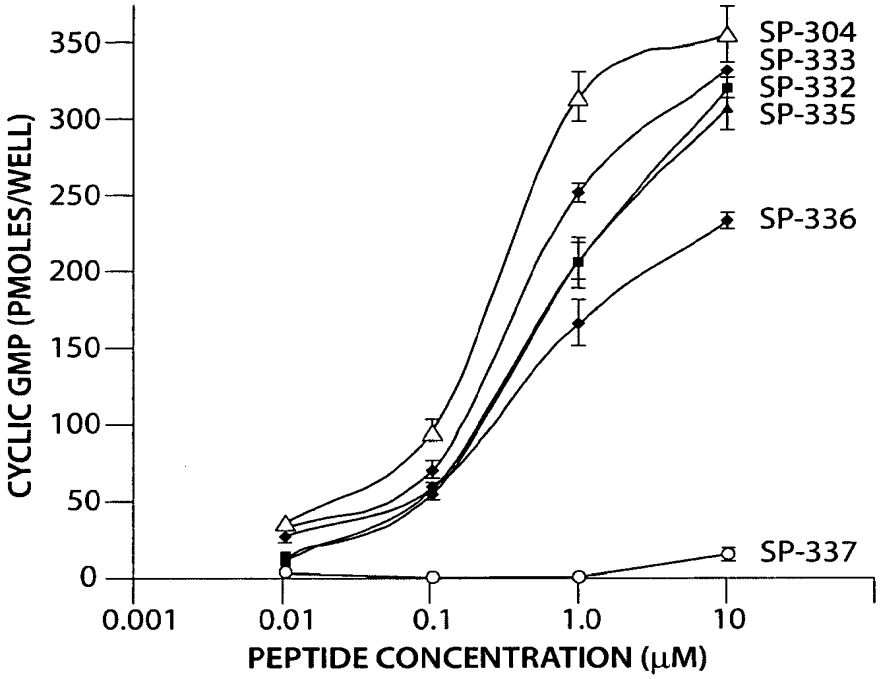
CYCLIC GMP (PMOLES/WELL)
350
300
250
200
150
100
50
0
0.001
0.01
0.1
1.0
10
PEPTIDE CONCENTRATION (μM)
SP-304
SP-333
SP-332
SP-335
SP-336
SP-337

Fig. 5

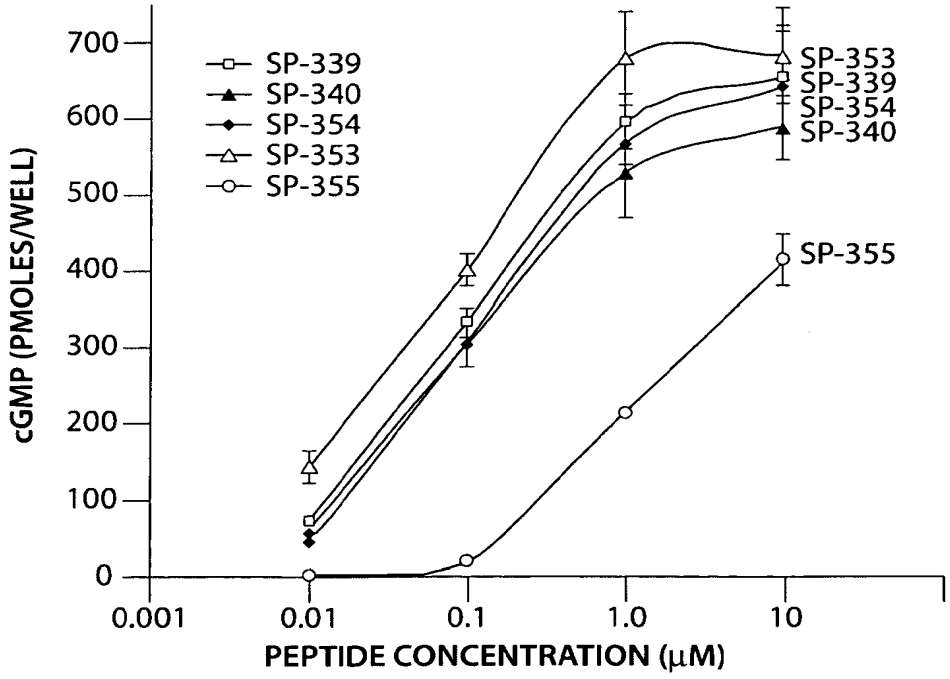
cGMP (PMOLES/WELL)
700
600
500
400
300
200
100
0
0.001
0.01
0.1
1.0
10
PEPTIDE CONCENTRATION (μM)
SP-339
SP-340
SP-354
SP-353
SP-355
SP-353
SP-339
SP-354
SP-340
SP-355

Fig. 6

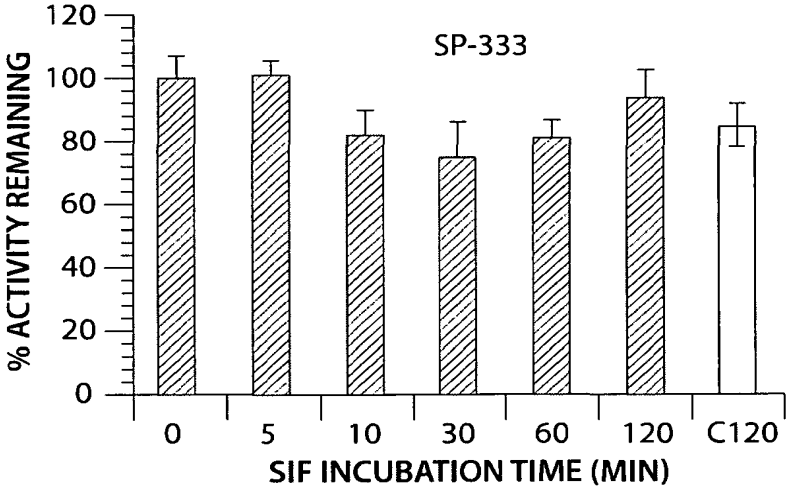
SP-333
% ACTIVITY REMAINING
120
100
80
60
40
20
0
0
5
10
30
60
120
C120
SIF INCUBATION TIME (MIN)

Fig. 7A

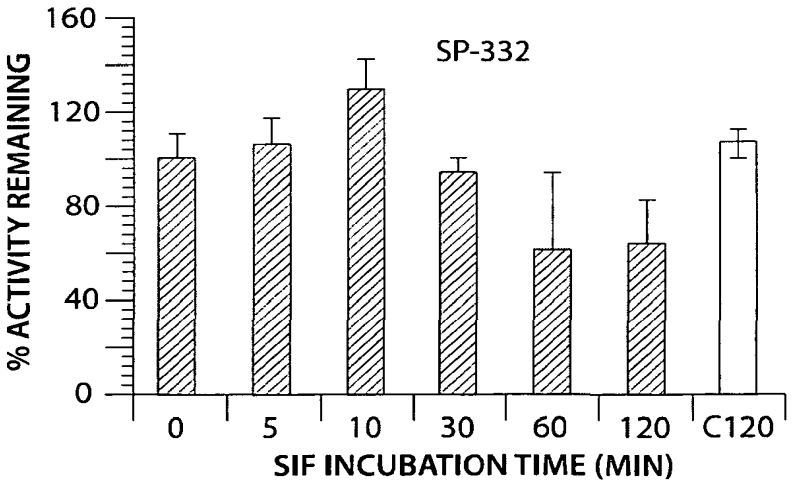
SP-332
% ACTIVITY REMAINING
160
120
80
40
0
0
5
10
30
60
120
C120
SIF INCUBATION TIME (MIN)

Fig. 7B

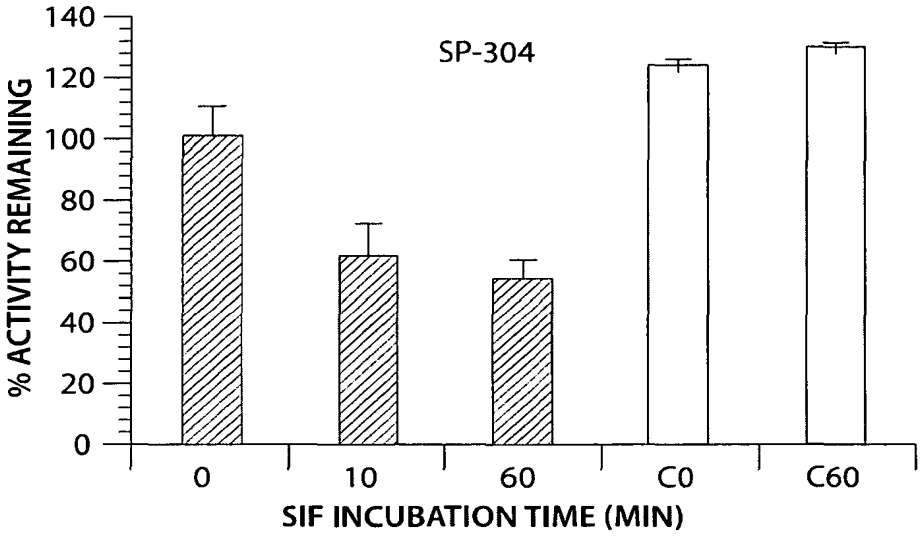

Fig. 7C

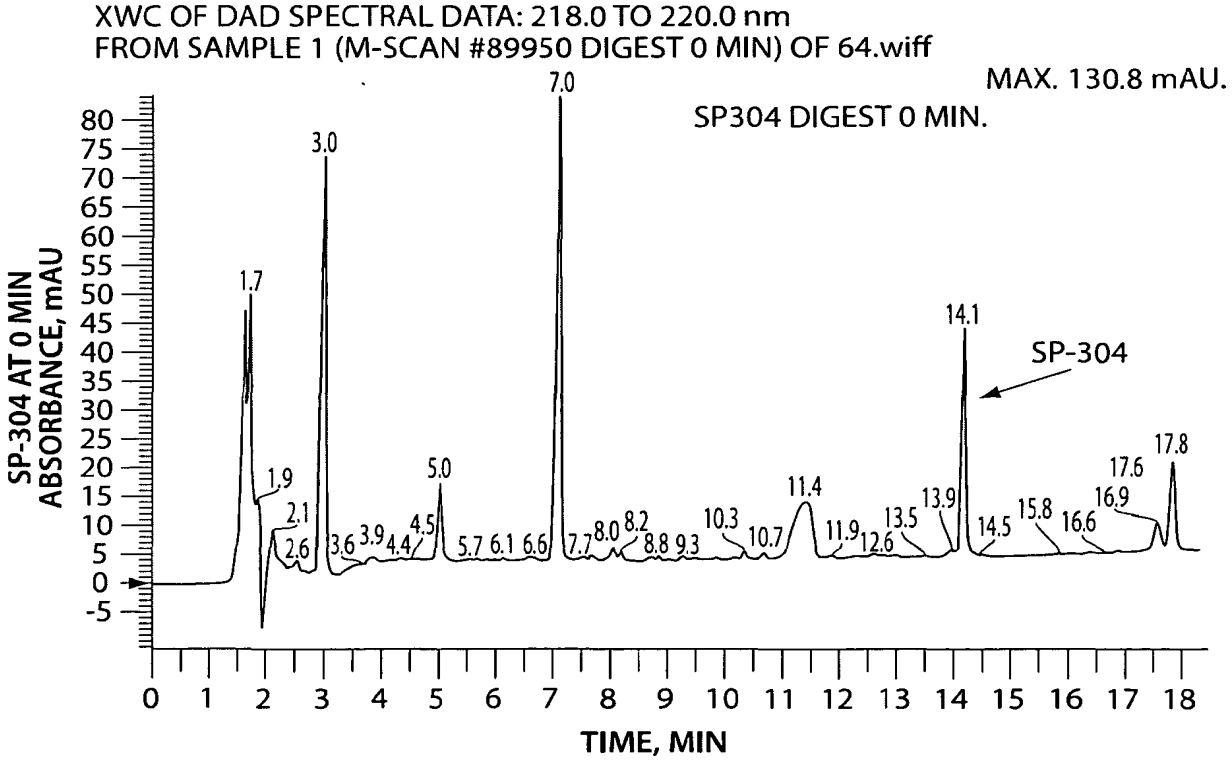

Fig. 7D-1

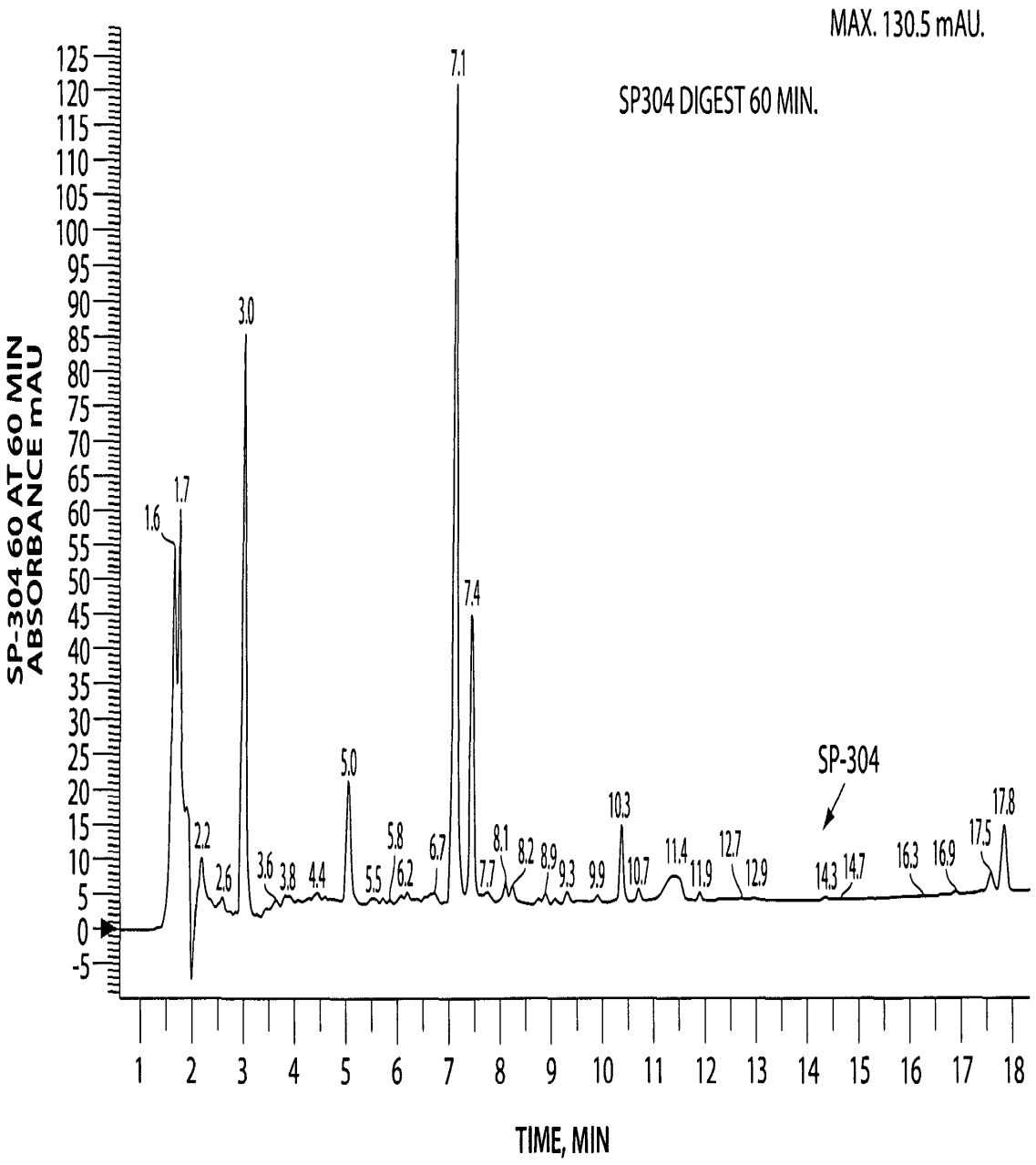

Fig. 7D-2

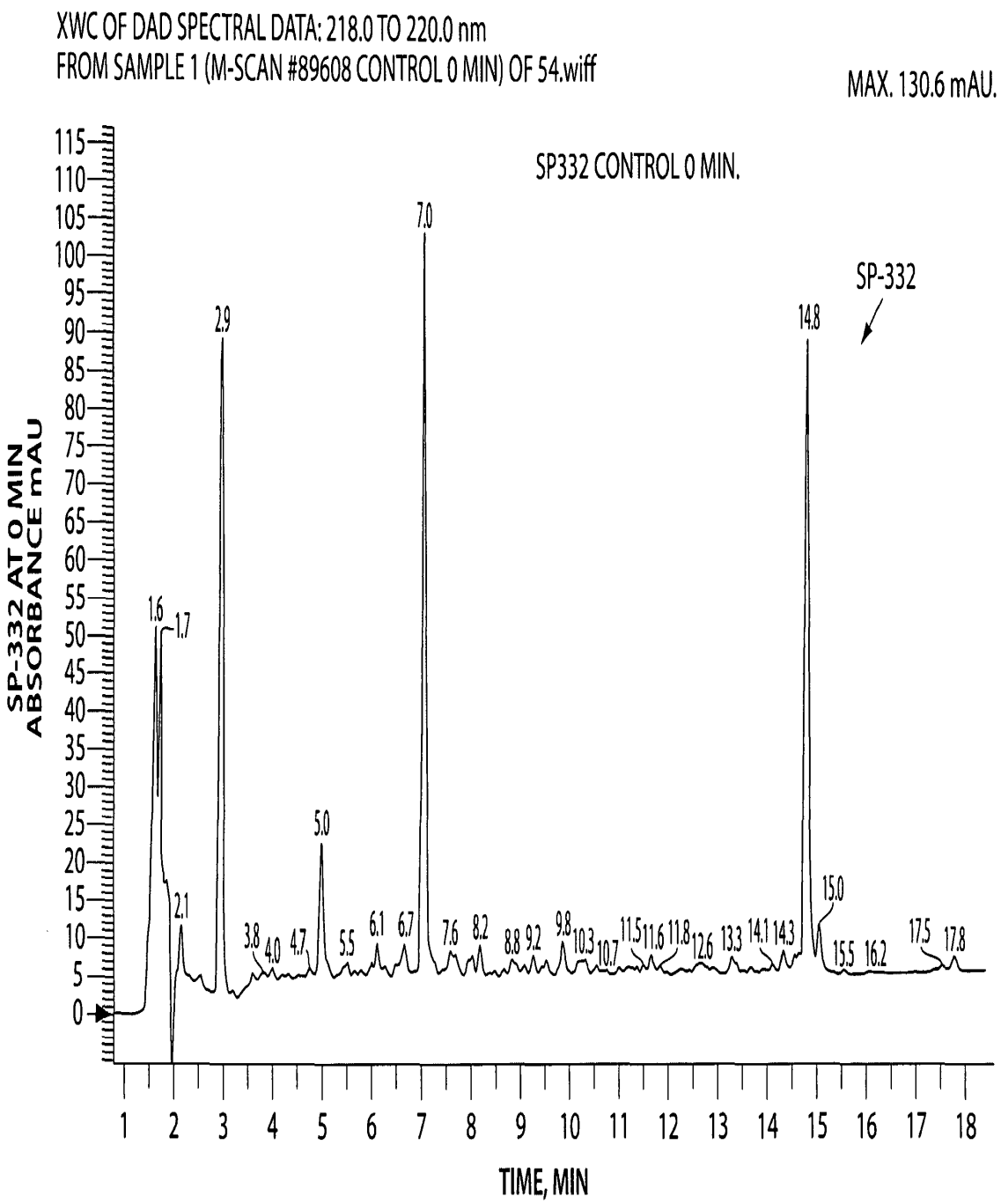

Fig. 7E-1

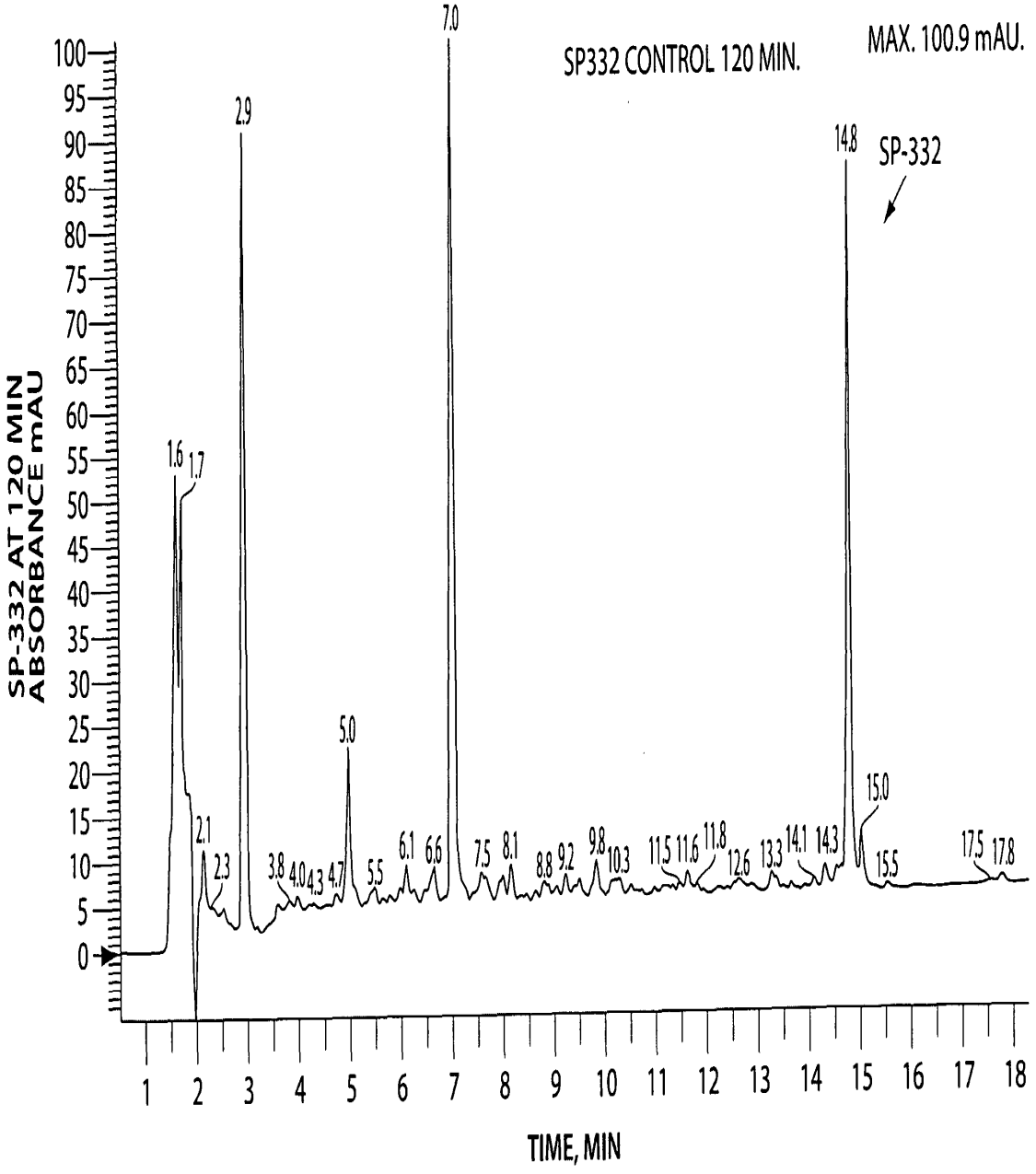

Fig. 7E-2

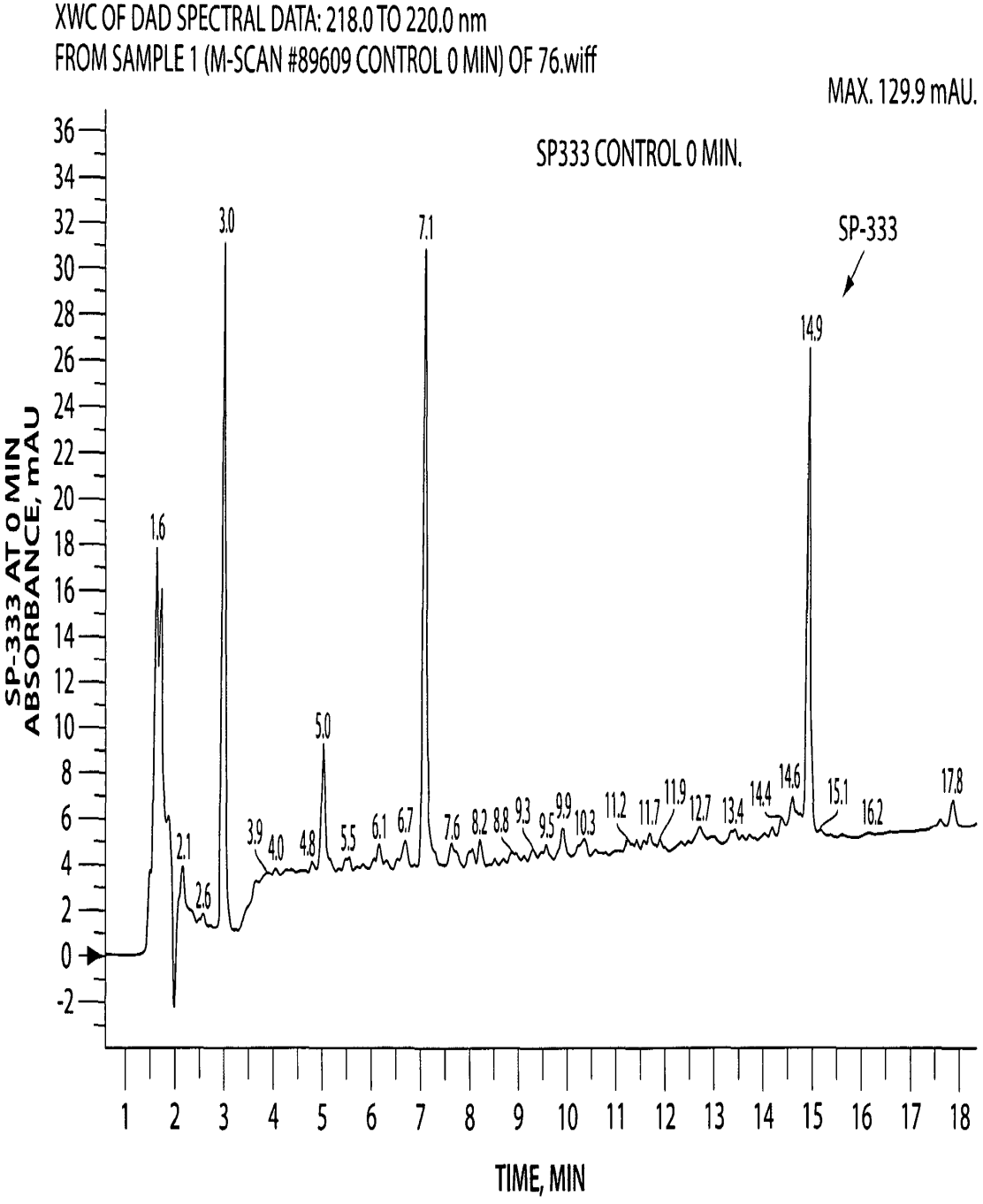

Fig. 7F-1

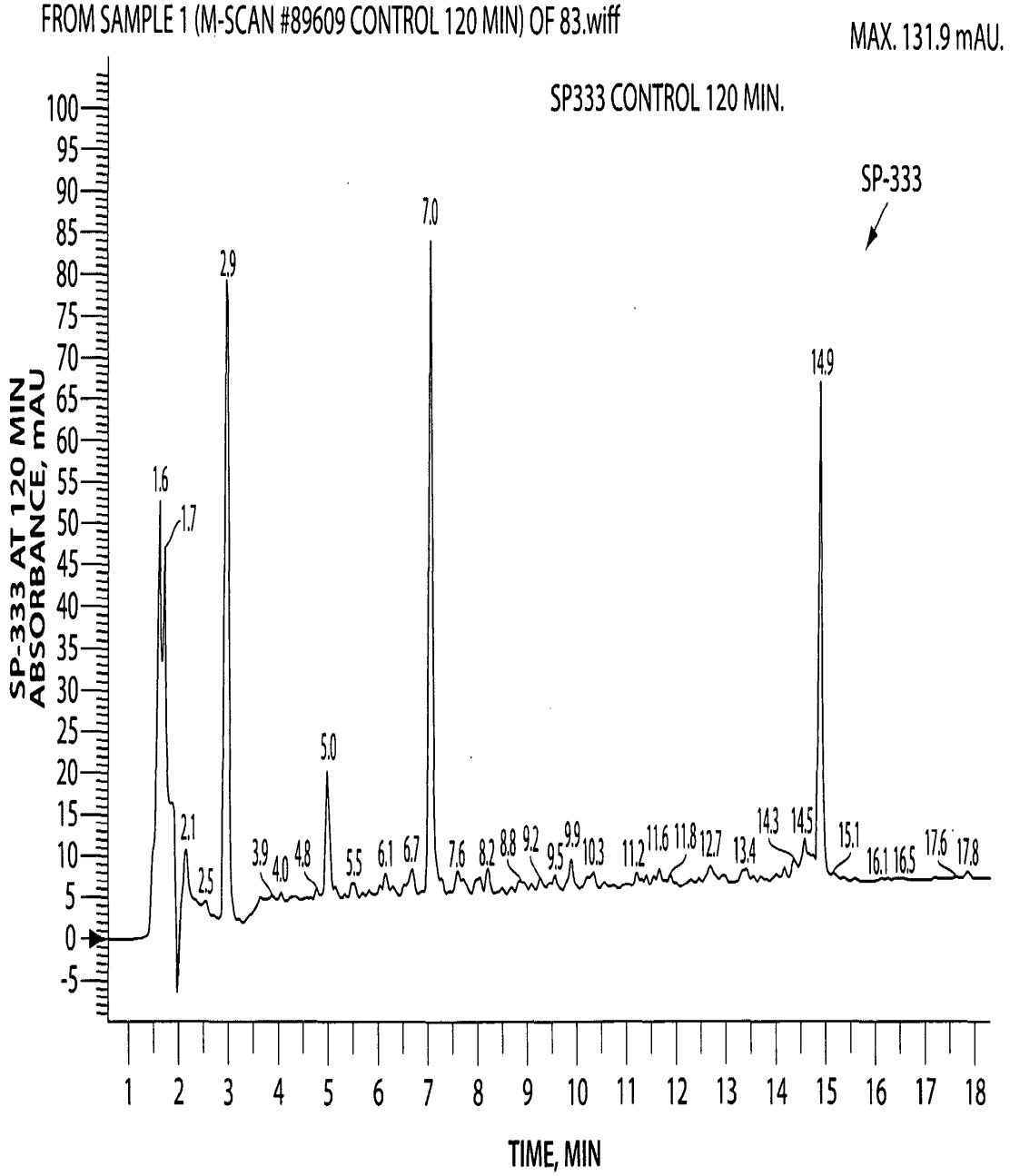

Fig. 7F-2

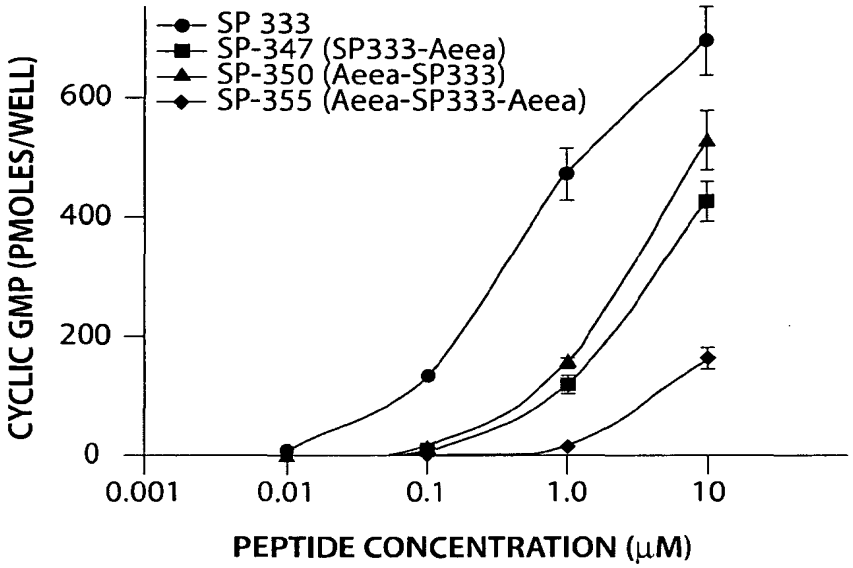
SP 333
SP-347 (SP333-Aeea)
SP-350 (Aeea-SP333)
SP-355 (Aeea-SP333-Aeea)
CYCLIC GMP (PMOLES/WELL)
600
400
200
0
0.001
0.01
0.1
1.0
10
PEPTIDE CONCENTRATION (μM)

Fig. 8

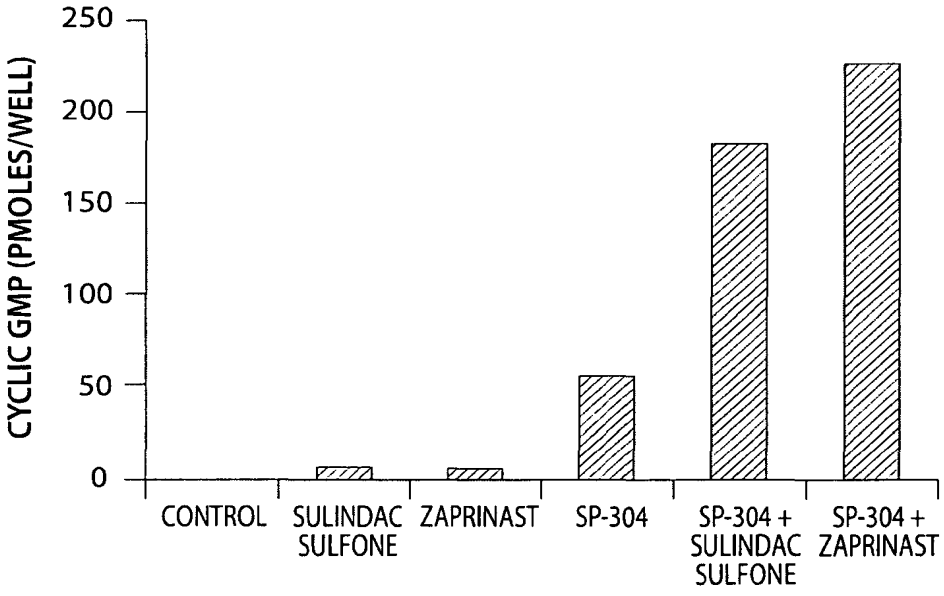
CYCLIC GMP (PMOLES/WELL)
250
200
150
100
50
0
CONTROL
SULINDAC SULFONE
ZAPRINAST
SP-304
SP-304 + SULINDAC SULFONE
SP-304 + ZAPRINAST

Fig. 9

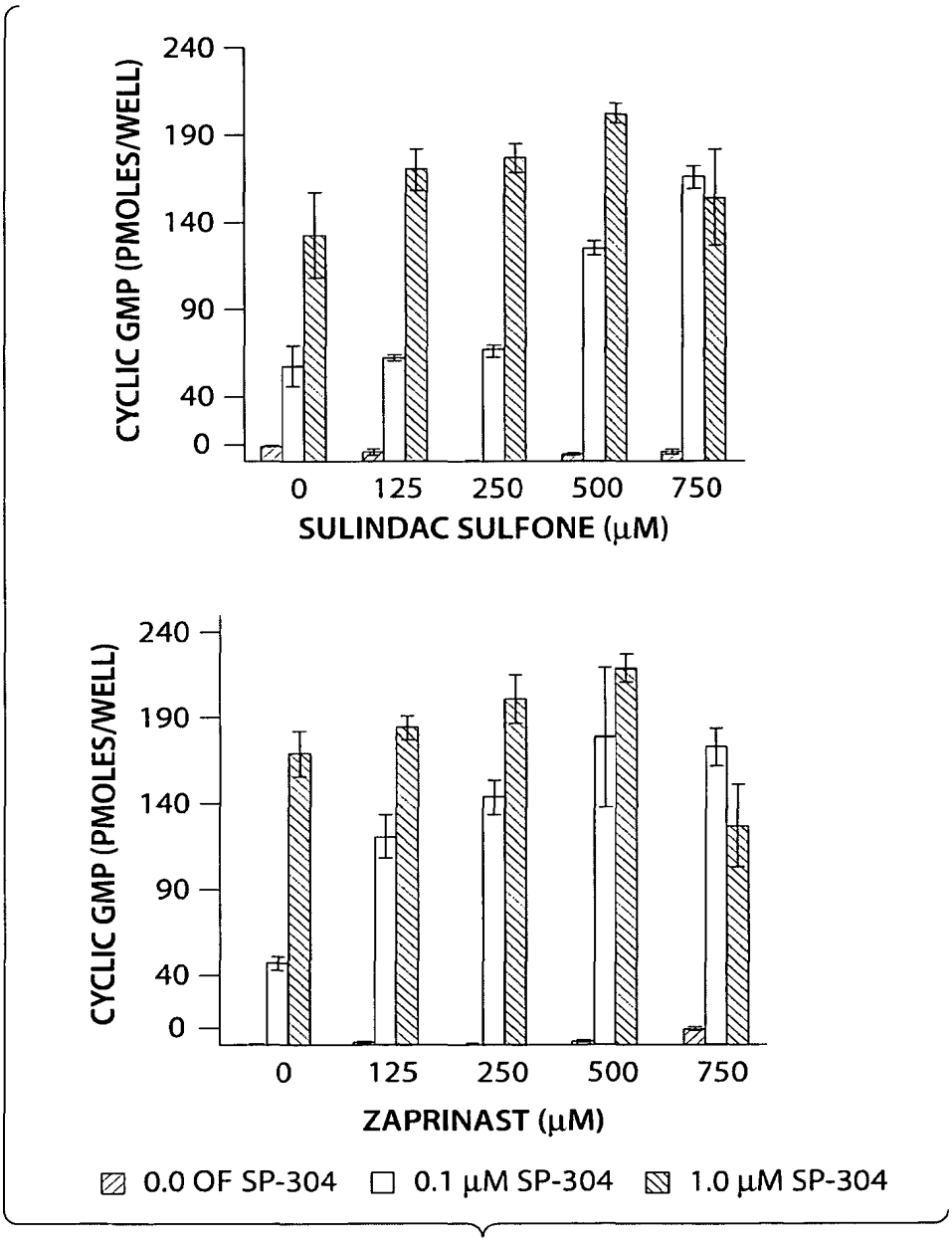
CYCLIC GMP (PMOLES/WELL)
240
190
140
90
40
0
0
125
250
500
750
SULINDAC SULFONE (μM)
CYCLIC GMP (PMOLES/WELL)
240
190
140
90
40
0
0
125
250
500
750
ZAPRINAST (μM)
0.0 OF SP-304
0.1 μM SP-304
1.0 μM SP-304

Fig. 10

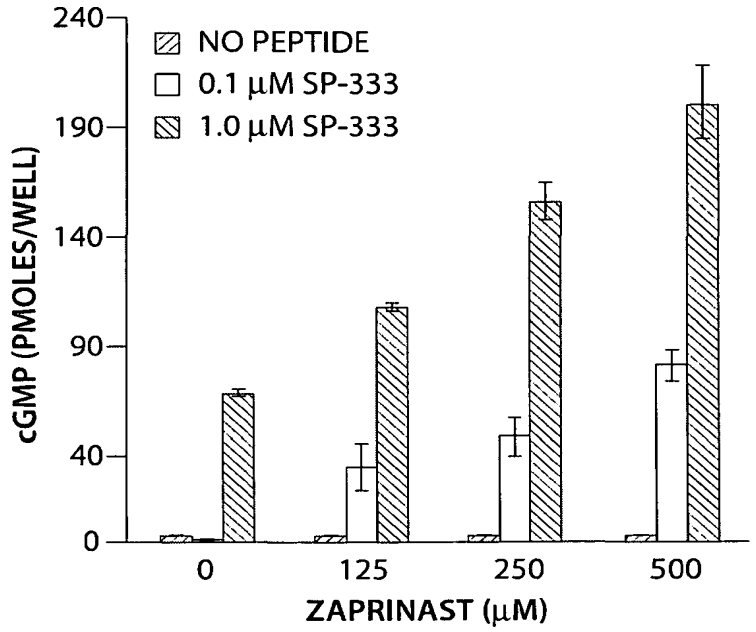
240
190
140
90
40
0
cGMP (PMOLES/WELL)
NO PEPTIDE
0.1 μM SP-333
1.0 μM SP-333
0
125
250
500
ZAPRINAST (μM)

Fig. 11

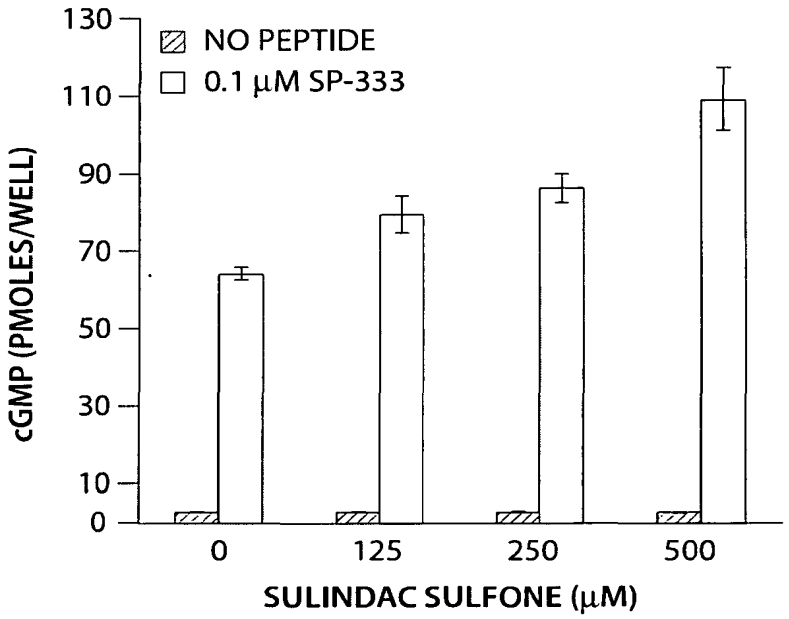
130
110
90
70
50
30
10
0
cGMP (PMOLES/WELL)
NO PEPTIDE
0.1 μM SP-333
0
125
250
500
SULINDAC SULFONE (μM)

Fig. 12

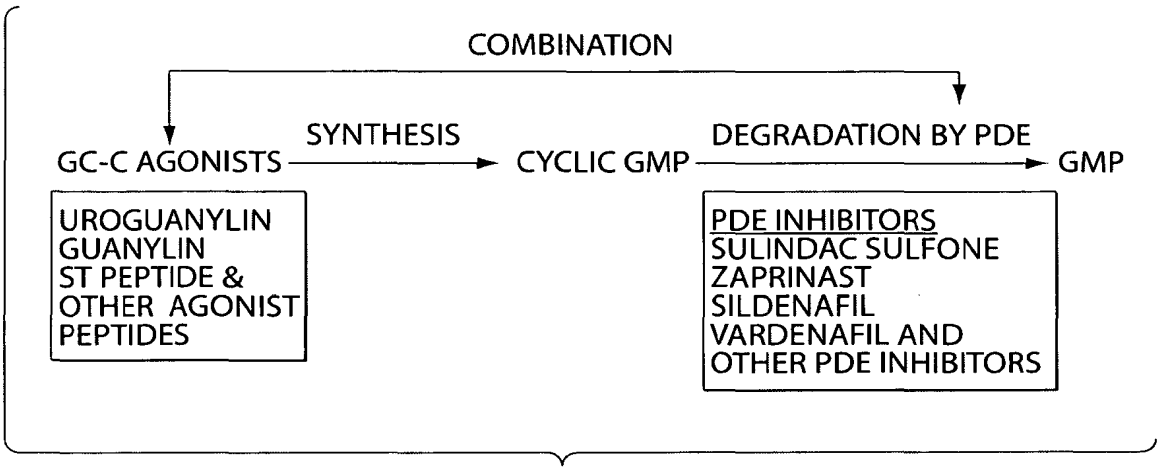
COMBINATION
SYNTHESIS
DEGRADATION BY PDE
GC-C AGONISTS
CYCLIC GMP
GMP
UROGUANYLIN
GUANYLIN
ST PEPTIDE &
OTHER AGONIST
PEPTIDES
PDE INHIBITORS
SULINDAC SULFONE
ZAPRINAST
SILDENAFIL
VARDENAFIL AND
OTHER PDE INHIBITORS

Fig. 13

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BIB DATA SHEET

CONFIRMATION NO. 2133

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
15/467,648	03/23/2017 RULE	424	1676	SYPA-009/C04US

APPLICANTS

SYNERGY PHARMACEUTICALS, INC., New York, NY

INVENTORS

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Rong FENG, Langhorne, PA;
John FOSS, Doylestown, PA;
Kunwar SHAILUBHAI, Audubon, PA;

**** CONTINUING DATA ***************************

This application is a CON of 14/845,644 09/04/2015 PAT 9610321
which is a CON of 14/661,299 03/18/2015 ABN
which is a CON of 13/421,769 03/15/2012 PAT 9616097
which is a CIP of PCT/US2011/051805 09/15/2011
which claims benefit of 61/383,156 09/15/2010
and claims benefit of 61/387,636 09/29/2010
and claims benefit of 61/392,186 10/12/2010

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
04/10/2017

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /JIA-HAI LEE/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		PA	6	17	2

ADDRESS

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004
UNITED STATES

TITLE

FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

FILING FEE RECEIVED		
930	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15467648	COMISKEY ET AL.
	Examiner	Art Unit
	JIA-HAI LEE	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

SEARCH NOTES		
Search Notes	Date	Examiner
EAST, Database: USPATFUL, USPGPUB, EPO, JPO, DERWENT, Search history enclosed	7/31/2017	JL
STN, Databases: Biosis, Embase, Medline, Caplus, Search history enclosed	7/31/2017	JL
PALM Inventor Search	7/31/2017	JL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	EAST, Database: USPATFUL,	7/31/2017	JL
	STN, Databases: Biosis, Embase, Medline, Caplus, Search history enclosed	7/31/2017	JL
	PALM Inventor Search	7/31/2017	JL

/J.L./ Examiner.Art Unit 1676	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15467648	COMISKEY ET AL.
	Examiner	Art Unit
	JIA-HAI LEE	1676

CPC						
Symbol					Type	Version
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A61K		45	/	06	I	2013-01-01
A61K		9	/	0053	I	2013-01-01
C07K		7	/	08	I	2013-01-01
C07K		7	/	64	I	2013-01-01
A61K		9	/	1623	I	2013-01-01
A61K		9	/	1652	I	2013-01-01
A61K		9	/	1676	I	2013-01-01
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			/			
			/			

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
			/					
			/					

/J.L./ Examiner.Art Unit 1676 (Assistant Examiner)	07/31/2017 (Date)	**Total Claims Allowed:** 16	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676 (Primary Examiner)	08/02/2017 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15467648	COMISKEY ET AL.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
		A	6	1	K	38 / 10 (2006.01.01)						
CROSS REFERENCE(S)												
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											

/J.L./ Examiner.Art Unit 1676	07/31/2017	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	16	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676	08/02/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15467648	COMISKEY ET AL.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1														
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/J.L./ Examiner.Art Unit 1676 (Assistant Examiner)	07/31/2017 (Date)	**Total Claims Allowed:** 16	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676 (Primary Examiner)	08/02/2017 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	14	NDECELCVNVACTGCL	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S2	2257	(Guanylate with Cyclase with C)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S3	9310	chromatographic with purity	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S4	2	S1 and S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S5	50	S2 and S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S6	4	S5 and @py<"2012"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S7	130	(Stephen near3 COMISKEY).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S8	306	(Rong near3 FENG).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S9	143	(John near3 FOSS).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S10	254	(Kunwar near3 SHAILUBHAI).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S11	0	(SYNERGY near3 PHARMACEUTICALS).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S12	718	S7 or S8 or S9 or S10	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54
S13	10	S12 and (S1 or S3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/07/31 09:54

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S14	14	NDECELCVNVACTGCL	US-PGPUB; USPAT	WITH	ON	2017/07/31 09:54
S15	6279	chromatographic with purity	US-PGPUB;	WITH	ON	2017/07/31

			USPAT			09:54
S16	2	S14 and S15	US-PGPUB; USPAT	WITH	ON	2017/07/31 09:54
S17	28	(Stephen near3 COMISKEY).in.	US-PGPUB; USPAT	WITH	ON	2017/07/31 09:54
S18	82	(Rong near3 FENG).in.	US-PGPUB; USPAT	WITH	ON	2017/07/31 09:54
S19	45	(John near3 FOSS).in.	US-PGPUB; USPAT	WITH	ON	2017/07/31 09:54
S20	76	(Kunwar near3 SHAILUBHAI).in.	US-PGPUB; USPAT	WITH	ON	2017/07/31 09:54
S21	0	(SYNERGY near3 PHARMACEUTICALS).in.	US-PGPUB; USPAT	WITH	ON	2017/07/31 09:54
S22	203	S17 or S18 or S19 or S20	US-PGPUB; USPAT	WITH	ON	2017/07/31 09:54
S23	0	S22 and S14	US-PGPUB; USPAT	WITH	ON	2017/07/31 09:54
S24	10	S22 and S15	US-PGPUB; USPAT	WITH	ON	2017/07/31 09:54

7/31/2017 10:17:48 AM
C:\Users\jlee24\Documents\EAST\Workspaces\15467648.wsp

(FILE 'HOME' ENTERED AT 10:07:36 ON 31 JUL 2017)

FILE 'REGISTRY' ENTERED AT 10:07:49 ON 31 JUL 2017

L1 82 SEA SPE=ON ABB=ON PLU=ON NDECELCVNVACTGCL/SQSP

L2 80 SEA SPE=ON ABB=ON PLU=ON L1 AND SQL=16

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE' ENTERED AT 10:09:15 ON 31 JUL 2017

L3 513 SEA SPE=ON ABB=ON PLU=ON (CHROMATOGRAPHIC PURITY)

L4 0 SEA SPE=ON ABB=ON PLU=ON (LOW MOISTURE CARRIER)

L5 107 SEA SPE=ON ABB=ON PLU=ON L2

L6 1 SEA SPE=ON ABB=ON PLU=ON L3 AND L5

L7 30 SEA SPE=ON ABB=ON PLU=ON COMISKEY STEPHEN/AU

L8 133 SEA SPE=ON ABB=ON PLU=ON FENG RONG/AU

L9 47 SEA SPE=ON ABB=ON PLU=ON FOSS JOHN/AU

L10 147 SEA SPE=ON ABB=ON PLU=ON SHAILUBHAI KUNWAR/AU

L11 285 SEA SPE=ON ABB=ON PLU=ON L7 OR L8 OR L9 OR L10

L12 25 SEA SPE=ON ABB=ON PLU=ON L11 AND L5

L13 1 SEA SPE=ON ABB=ON PLU=ON L12 AND L3

L14 1 SEA SPE=ON ABB=ON PLU=ON L6 OR L13

D L14 IBIB ABS HITSEQ

PTO/SB/30 (07-14)
Approved for use through 07/31/2016 OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	15/467,648
Filing Date	03/23/2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	Jia-Hai LEE
Attorney Docket Number	SYPA-009/C04US 321994-2341

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not compy with the requirements of 35 U.S.C 371, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO on page 2.)

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
      ii. ☐ Other _____

   b. ☒ Enclosed
      i. ☐ Amendment/Reply
      ii. ☐ Affidavit(s)/ Declaration(s)
      iii. ☒ Information Disclosure Statement (IDS)
      iv. ☐ Other _____

2. Miscellaneous

   Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a
   a. ☐ period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to
   a. ☒ Deposit Account No. 50-1283.
      i. ☒ RCE fee required under 37 CFR 1.17(e)
      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
      iii ☐ Other _____
   b. ☐ Check in the amount of $ _____ enclosed
   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Anne E Fleckenstein/	Date	November 8, 2017
Name (Print/Type)	Anne E. Fleckenstein	Registration No.	62951

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature			
Name (Print/Type)		Date	

PTO/SB/30 (07-14)
Approved for use through 07/31/2016 OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Instruction Sheet for RCEs

(not to be submitted to the USPTO)

NOTES:

An RCE is not a new application, and filing an RCE will not result in an application being accorded a new filing date.

Filing Qualifications:

The application must be a utility or plant application filed on or after June 8, 1995. The application cannot be a provisional application, a utility or plant application filed before June 8, 1995, an international application that does not comply with the requirements of 35 U.S.C. 371, a design application, or a patent under reexamination. See 37 CFR 1.114(e). An international application does not comply with the requirements of 35 U.S.C. 371 until the requirements under 35 U.S.C. 371(c), including the requirement for the inventor's oath or declaration under 35 U.S.C. 371(c)(4), have been complied with.

Filing Requirements:

Prosecution in the application must be closed. Prosecution is closed if the application is under appeal, or the last Office action is a final action, a notice of allowance, or an action that otherwise closes prosecution in the application (e.g., an Office action under *Ex parte Quayle*). See 37 CFR 1.114(b).

A submission and a fee are required at the time the RCE is filed. If reply to an Office action under 35 U.S.C. 132 is outstanding (e.g., the application is under final rejection), the submission must meet the reply requirements of 37 CFR 1.111. If there is no outstanding Office action, the submission can be an information disclosure statement, an amendment, new arguments, or new evidence. See 37 CFR 1.114(c). The submission may be a previously filed amendment (e.g., an amendment after final rejection).

WARNINGS:

Request for Suspension of Action:

All RCE filing requirements must be met before suspension of action is granted. A request for a suspension of action under 37 C FR 1.103(c) does not satisfy the submission requirement and does not permit the filing of the required submission to be suspended.

Improper RCE will NOT toll Any Time Period:

Before Appeal **-** If the RCE is improper (e.g., prosecution in the application is not closed or the submission or fee has not been filed) and the application is not under appeal, the time period set forth in the last Office action will continue to run and the application will be abandoned after the statutory time period has expired if a reply to the Office action is not timely filed. No additional time will be given to correct the improper RCE.

Under Appeal **-** If the RCE is improper (e.g., the submission or the fee has not been filed) and the application is under appeal, the improper RCE is effective to withdraw the appeal. Withdrawal of the appeal results in the allowance or abandonment of the application depending on the status of the claims. If there are no allowed claims, the application is abandoned. If there is at least one allowed claim, the application will be passed to issue on the allowed claim(s). See MPEP 1215.01.

See MPEP 706.07(h) for further information on the RCE practice.

Electronic Patent Application Fee Transmittal

Application Number:	15467648
Filing Date:	23-Mar-2017
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Filer:	Anne Elizabeth Fleckenstein
Attorney Docket Number:	SYPA-009C04US 321994-2341

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 1st Request	2801	1	600	600
		Total in USD ($)		**600**

Electronic Acknowledgement Receipt

EFS ID:	30849426
Application Number:	15467648
International Application Number:	
Confirmation Number:	2133
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009C04US 321994-2341
Receipt Date:	08-NOV-2017
Filing Date:	23-MAR-2017
Time Stamp:	14:44:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$600
RAM confirmation Number	110917INTEFSW00001060501283
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	SYPA_009_C04US_SB08.pdf	349036 b874abf8d0dcf595974b3e01ce2635479a742cc6	no	19
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
2	Transmittal Letter	SYPA-009_C04US_2017-11-08_IDS.pdf	113027 0747cad82cfa9760d7ccd8e7b190a684bacd48ad	no	4
Warnings:					
Information:					
3	Request for Continued Examination (RCE)	SYPA-009_C04US_2017-11-08_RCE.pdf	177717 35c997ca5f40ba2a4f07a0b3089b8e9382aa6e4d	no	2
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30594 71ad34704123a476712d796c5a50b55d164a3ff4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	670374		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (07-09)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	5,106,834	04-21-1992	Bovy et al.	
	2.	5,130,333	07-14-1992	Pan et al.	
	3.	5,489,670	02-06-1996	Currie et al.	
	4.	5,518,888	05-21-1996	Waldman et al.	
	5.	5,578,709	11-26-1996	Woiszwillo et al.	
	6.	5,601,990	02-11-1997	Waldman et al.	
	7.	5,721,238	02-24-1998	Heiker et al.	
	8.	5,731,159	03-24-1998	Waldman et al.	
	9.	5,817,624	10-06-1998	Yang et al.	
	10.	5,879,656	03-09-1999	Waldman et al.	
	11.	5,928,873	07-29-1999	Waldman et al.	
	12.	5,969,097	10-19-1999	Wiegand et al.	
	13.	6,060,037	05-09-2000	Waldman et al.	
	14.	6,235,782	05-22-2001	Pamukcu et al.	
	15.	7,041,786	05-09-2006	Shailubhai et al.	
	16.	7,067,748	07-20-2006	Whitmore, Jr. et al.	
	17.	7,375,083	05-20-2008	Mickle et al.	
	18.	7,494,979	02-24-2009	Currie et al.	
	19.	7,799,897	09-21-2010	Jacob et al.	
	20.	7,879,802	02-01-2011	Shailubhai et al.	
	21.	8,034,782	10-11-2011	Shailubhai	
	22.	8,114,831	02-14-2012	Shailubhai et al.	
	23.	8,207,295	06-26-2012	Shailubhai et al.	
	24.	8,357,775	01-22-2013	Shailubhai et al.	
	25.	8,367,800	02-05-2013	Shailubhai	
	26.	8,497,348	07-30-2013	Shailubhai et al.	
	27.	8,569,246	10-29-2013	Shailubhai	
	28.	8,637,451	01-28-2014	Shailubhai et al.	
	29.	8,664,354	03-04-2014	Shailubhai	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.
SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	30.	8,716,224	05-06-2014	Shailubhai et al.	
	31.	8,901,075	12-02-2014	Shailubhai et al.	
	32.	8,969,514	03-03-2015	Shailubhai	
	33.	9,238,677	01-19-2016	Shailubhai et al.	
	34.	9,266,926	02-23-2016	Shailubhai et al.	
	35.	9,486,494	11-08-2016	Shailubhai	
	36.	9,545,446	01-17-2016	Riff et al.	
	37.	2002/0128176 A1	09-12-2002	Forssmann et al.	
	38.	2002/0133168 A1	09-19-2002	Smeldley et al.	
	39.	2002/0143015 A1	10-03-2002	Fryburg et al.	
	40.	2003/0073628 A1	04-17-2003	Shailubhai et al.	
	41.	2004/0015140 A1	01-22-2004	Shields	
	42.	2005/0016244 A1	01-27-2005	Hergemoller	
	43.	2005/0032684 A1	02-10-2005	Cetin et al.	
	44.	2005/0107734 A1	05-19-2005	Coroneo	
	45.	2005/0145351 A1	07-07-2005	Schaible, et al.	
	46.	2005/0266047 A1	12-01-2005	Tu et al	
	47.	2005/0267297 A1	12-01-2005	Berlin	
	48.	2006/0086653 A1	04-27-2006	St. Germain	
	49.	2006/0094658 A1	05-04-2006	Currie	
	50.	2007/0101158 A1	05-03-2007	Elliott	
	51.	2008/0137318 A1	06-12-2008	Rangaraj et al.	
	52.	2008/0151257 A1	06-26-2008	Yasuda et al.	
	53.	2009/0048175 A1	02-19-2009	Shailubhai et al.	
	54.	2009/0192083 A1	07-30-2009	Currie	
	55.	2009/0253634 A1	10-08-2009	Currie et al.	
	56.	2010/0048489 A1	02-25-2010	Fretzen	
	57.	2010/0069306 A1	03-18-2010	Shailubhai et al.	
	58.	2010/0093635 A1	04-15-2010	Shailubhai	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	78.	JP 2009-519343 A (corresponds to WO 2007/070562 A2)	05-14-2009			

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Sheet 4 of 19

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Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

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	98.	WO 2008/137318 A1	11-13-2008	IRONWOOD PHARMACEUTICALS, INC.		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 6 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

NON PATENT LITERATURE DOCUMENTS

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 7 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

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Art Unit	1676
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	147.	European Patent 1,379,224: Written submission dated November 22, 2011 (18 pages)	
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Sheet 10 of 19

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Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

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Sheet 11 of 19

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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 17 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	251.	SHAILUBHAI "SP-304 to treat GI disorders- effects of a single, oral dose of SP-304 in safety, tolerability, pharmacokinetics and pharmacodynamics in healthy volunteers" [Abstract]: in Digestive Disease Week, (2009) 1 page.	
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	275.	Written Opinion of the International Searching Authority, PCT Appl. No. PCT/US2011/051805, 5 pages (June 21, 2012)	

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Docket No.: SYPA-009/C04US 321994-2341
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Stephen COMISKEY	Confirmation No.:	2133
Application No.:	15/467,648	Group Art Unit:	1676
Filed:	March 23, 2017	Examiner:	LEE, Jia-Hai

For: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

Via EFS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §§ 1.56, 1.97, AND 1.98

In accordance with the duty of disclosure set forth in 37 C.F.R. §1.56, Applicant hereby submits the following information in conformance with 37 C.F.R. §§1.97 and 1.98. It is respectfully requested that the information be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

[] Pursuant to 37 C.F.R. §1.98, copies of non-US patent documents, Cite Nos., cited in the attached Form used in lieu of PTO/SB/08 are enclosed.

[X] Copies of the publications listed on the attached Form used in lieu of PTO/SB/08 are **not** being provided pursuant to 37 C.F.R. §1.98(d) because the publications were previously cited by or submitted to the Office in **prior Applications Serial No(s). 14/845,644 (U.S. Patent No. 9,610,321), 14/661,299 and 13/421,769 (U.S. Patent No. 9,616,097)** to which the above-identified application claims priority under 35 U.S.C. §120.

[X] No copies of any U.S. patents or U.S. patent application publications listed on the attached Form used in lieu of PTO/SB/08 are being provided pursuant to 37 C.F.R. §1.98.

[] Publication(s) listed on the attached Form used in lieu of PTO/SB/08 were cited in a foreign search or examination report corresponding to application serial no. and mailed on .

[] Enclosed is a copy of a non-English publication(s) _____ Pursuant to §609 of the M.P.E.P., Applicant submits the attached foreign search or examination report, which cites such non-English language publication(s).

[] Enclosed is a copy of a non-English publication(s) _____ English language publication _____ (copy enclosed) claims priority from this non-English publication.

[] Enclosed is an explanation of non-English publication(s) _____ for which an English translation is not available.

[] Enclosed is an English translation of non-English publication(s) _____ cited in the attached Form used in lieu of PTO/SB/08.

[] Enclosed is a copy of pending patent Application Serial No. _____.

[X] In accordance with **37 C.F.R. §1.97(b)**, no additional fee for submission of this Information Disclosure Statement is required, as it is filed within any one of the following time periods:

[] within three months from the filing date of this national application other than a CPA under 37 C.F.R. § 1.53(d);

[] within three months from the date of entry of the national stage as set forth in 37 C.F.R. §1.491 in this international application;

[] before the mailing date of a first office action on the merits; or

[X] before the mailing of a first office action after the filing of a request for continued examination under 37 C.F.R. § 1.114.

[] In accordance with **37 C.F.R. §1.97(c)**, this Information Disclosure Statement is filed after the period specified in 37 C.F.R. § 1.97(b), but before the mailing of any of the following:

[] a final action under 37 C.F.R. §1.113;

[] a notice of allowance under 37 C.F.R. §1.311; or

[] an action that otherwise closes prosecution in this application.

In accordance with 37 C.F.R. §1.97(c) also enclosed is:

[] Fee under 37 C.F.R. §1.17(p) in the amount of $180.00;

[] Fee under 37 C.F.R. §1.17(p) in the amount of $90.00;

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[] Statement as specified in 37 C.F.R. §1.97(e):

[] Each item of information contained in the Information Disclosure Statement cited herein was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing date of the Information Disclosure Statement; or

[] No item of information contained in the Information Disclosure Statement submitted herewith was cited in any communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, having made a reasonable inquiry, no item of information contained in the Information Disclosure Statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three months prior to the filing date of the Information Disclosure Statement.

[] In accordance with **37 C.F.R. §1.97(d)**, this Information Disclosure Statement is filed after the period specified in 37 C.F.R. § 1.97(c), but with or before the payment of the issue fee.

In accordance with 37 C.F.R. §1.97(d) also enclosed is:

[] Fee under 37 C.F.R. §1.17(p) in the amount of $180.00;

[] Fee under 37 C.F.R. §1.17(p) in the amount of $90.00; or

[] Fee under 37 C.F.R. §1.17(p) in the amount of $45.00;

and

[] Statement as specified in 37 C.F.R. §1.97(e):

[] Each item of information contained in the Information Disclosure Statement cited herein was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing date of the Information Disclosure Statement; or

[] No item of information contained in the Information Disclosure Statement submitted herewith was cited in any communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, having made a reasonable inquiry, no item of information contained in the Information Disclosure Statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three months prior to the filing date of the Information Disclosure Statement.

[] In accordance with **37 C.F.R. § 1.704(d)**, Applicant notes that to our knowledge each item of information contained in the information disclosure statement:

[] was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § **1.56(c)** more than thirty days prior to the filing of the information disclosure statement.

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received by any individual designated in § **1.56(c)** more than thirty days prior to the filing of the information disclosure statement.

In accordance with 37 C.F.R. § 1.97(g), this Information Disclosure Statement shall not be construed as to mean that a search has been made.

In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be material to patentability as defined by 37 C.F.R § 1.56(b).

Remarks

It is respectfully requested that the Examiner consider the above-noted information and return an initialed copy of the attached Form used in lieu of PTO/SB/08 to the undersigned.

The Director is hereby requested and authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 50-1283 which the undersigned is authorized to draw.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Dated: November 8, 2017

Respectfully submitted,
COOLEY LLP

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004

Tel: (202) 842-7800
Fax: (202) 842-7899

By: /Anne E Fleckenstein/
Anne E. Fleckenstein
Reg. No. 62,951

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/J.L/	1.	5,106,834	04-21-1992	Bovy et al.	
/J.L/	2.	5,130,333	07-14-1992	Pan et al.	
/J.L/	3.	5,489,670	02-06-1996	Currie et al.	
/J.L/	4.	5,518,888	05-21-1996	Waldman et al.	
/J.L/	5.	5,578,709	11-26-1996	Woiszwillo et al.	
/J.L/	6.	5,601,990	02-11-1997	Waldman et al.	
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/J.L/	29.	8,664,354	03-04-2014	Shailubhai	

Examiner Signature	/JIA-HAI LEE/	Date Considered	12/19/2017

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/J.L/	30.	8,716,224	05-06-2014	Shailubhai et al.	
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Examiner Signature	/JIA-HAI LEE/	Date Considered	12/19/2017

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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Examiner Signature	/JIA-HAI LEE/	Date Considered	12/19/2017

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 4 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

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Examiner Signature	/JIA-HAI LEE/	Date Considered	12/19/2017

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Sheet 5 of 19

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Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

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Examiner Signature	/JIA-HAI LEE/	Date Considered	12/19/2017

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Sheet 6 of 19

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First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

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Examiner Signature	/JIA-HAI LEE/	Date Considered	12/19/2017

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Filing Date	March 23, 2017
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Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

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/J.L/	144.	European Patent 1,379,224: Response to Communication from Opposition division dated October 8, 2010 (44 pages)	
/J.L/	145.	European Patent 1,379,224: Written submission dated December 7, 2011 (6 pages)	
/J.L/	146.	European Patent 1,379,224: Written submission dated November 18, 2011 by Ironwood (14 pages)	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 9 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

NON PATENT LITERATURE DOCUMENTS

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/J.L/	147.	European Patent 1,379,224: Written submission dated November 22, 2011 (18 pages)	
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Art Unit	1676
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Attorney Docket Number	SYPA-009/C04US 321994-2341

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
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Examiner Signature	/JIA-HAI LEE/	Date Considered	12/19/2017

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Sheet 16 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

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Examiner Signature	/JIA-HAI LEE/	Date Considered	12/19/2017

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/J.L/	251.	SHAILUBHAI "SP-304 to treat GI disorders- effects of a single, oral dose of SP-304 in safety, tolerability, pharmacokinetics and pharmacodynamics in healthy volunteers" [Abstract]: in Digestive Disease Week, (2009) 1 page.	
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Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
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/J.L/	277.	WU "Atrial natriuretic peptide induces apoptosis in neonatal rat cardia myocytes" J. Biol. Chem. 272(23):14860-14866 (1997)	
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/467,648	COMISKEY et al.
	Examiner	Art Unit
	JIA-HAI LEE	1676

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

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Search Notes		
Search Notes	Date	Examiner
EAST, Database: USPATFUL, USPGPUB, EPO, JPO, DERWENT, Search history enclosed	12/19/2017	JL
PALM Inventor Search	12/19/2017	JL

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	EAST, Database: USPATFUL,	12/19/2017	JL
	PALM Inventor Search	12/19/2017	JL

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58249 7590 01/08/2018

COOLEY LLP
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1299 Pennsylvania Avenue, NW
Suite 700
Washington, DISTRICT OF COLUMBIA 20004

EXAMINER
LEE, JIA-HAI

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 01/08/2018

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/467,648	03/23/2017	Stephen COMISKEY	SYPA-009C04US 321994-2341	2133

TITLE OF INVENTION: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
REGULAR	SMALL	$480	$0.00	$0.00	$480	04/09/2018

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(Date)

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EXAMINER	ART UNIT	CLASS-SUBCLASS
LEE, JIA-HAI	1676	424-451000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

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4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/467,648	03/23/2017	Stephen COMISKEY	SYPA-009C04US ~~321994-2341~~	2133

58249 7590 01/08/2018

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DISTRICT OF COLUMBIA 20004

EXAMINER	
LEE, JIA-HAI	

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 01/08/2018

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/467,648	Applicant(s) COMISKEY et al.	
	Examiner JIA-HAI LEE	Art Unit 1676	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 11/8/2017 .
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____ .

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-16 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 11/08/2017
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____ .
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____ .

/J.L/ Examiner, Art Unit 1676	/SATYANARAYANA R GUDIBANDE/ Primary Examiner, Art Unit 1676

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11/08/2017 has been entered.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 11/08/2017 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Examiner's Comment

Applicant filed RCE for consideration of new references. The references do not teach or suggest the previously allowed claims.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

The closest prior art reference Shailubhai et al. (Digestive Disease Week. San Diego: 2008) taught the use of a per unit dose of a [4, 12; 7, 15] bicyclic peptide consisting of SEQ ID NO: 1 (named SP-304) in a clinical trial, but the reference did not teach or suggest the composition further comprising an inert low moisture carrier and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91 % after storage for at least three months as claimed.

The other closest reference Shailubhai et al. (WO 2008/151257 A2) suggest the use of SP-304 to treat gastrointestinal disorders comprising irritable bowel syndrome (IBS) and constipation (p5, line 8-21). Shailubhai et al. further suggest the oral composition comprising a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch and/or a lubricant such as magnesium stearate or Sterotes (p41, line 19-30). However, Shailubhai et al. did not teach the composition consisting of SP-304, an inert low moisture carrier and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91 % after storage for at least three months as claimed.

Since applicant filed terminal disclaimers against the previously issued patents US 9,610,321B2 and US 9,616,097 B2 as well as the co-pending application No. 15/467,631, this instant application is allowable.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to JIA-HAI LEE whose telephone number is (571)270-1691. The examiner can normally be reached on Mon-Fri 9:00-6:00.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kartheinz R Skowronek can be reached on 571-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1676

19-December-2017

/SATYANARAYANA R GUDIBANDE/
Primary Examiner, Art Unit 1676

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/467,648	COMISKEY et al.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

CPC						
Symbol					**Type**	**Version**
A61K	/	38	/	10	F	2013-01-01
A61K	/	47	/	38	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61K	/	45	/	06	I	2013-01-01
A61K	/	9	/	0053	I	2013-01-01
C07K	/	7	/	08	I	2013-01-01
C07K	/	7	/	64	I	2013-01-01
A61K	/	9	/	1623	I	2013-01-01
A61K	/	9	/	1652	I	2013-01-01
A61K	/	9	/	1676	I	2013-01-01
A61K	/	9	/	4858	I	2013-01-01
A61K	/	9	/	4866	I	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

/J.L./ Examiner.Art Unit 1676	19 December 2017	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	16	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676	22 December 2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/467,648	COMISKEY et al.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	10	/	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/J.L./ Examiner.Art Unit 1676	19 December 2017	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	16	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676	22 December 2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/467,648	COMISKEY et al.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	10	10												
2	2	11	11												
3	3	12	12												
4	4	13	13												
5	5	14	14												
6	6	15	15												
7	7	16	16												
8	8														
9	9														

/J.L./ Examiner.Art Unit 1676	19 December 2017	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	16	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676	22 December 2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	15	NDECELCVNVACTGCL	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S2	2344	(Guanylate with Cyclase with C)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S3	9660	chromatographic with purity	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S4	2	S1 and S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S5	51	S2 and S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S6	4	S5 and @py<"2012"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S7	130	(Stephen near3 COMISKEY).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S8	312	(Rong near3 FENG).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S9	144	(John near3 FOSS).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S10	268	(Kunwar near3 SHAILUBHAI).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S11	0	(SYNERGY near3 PHARMACEUTICALS).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S12	739	S7 or S8 or S9 or S10	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S13	10	S12 and (S1 or S3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:42
S14	9660	chromatographic with purity	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:45
S15	2	S1 and S14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/12/19 13:45
S16	51	S2 and S14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT;	WITH	ON	2017/12/19 13:46

			IBM_TDB			

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S17	15	NDECELCVNVACTGCL	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42
S18	6473	chromatographic with purity	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42
S19	2	S17 and S18	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42
S20	28	(Stephen near3 COMISKEY).in.	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42
S21	83	(Rong near3 FENG).in.	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42
S22	46	(John near3 FOSS).in.	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42
S23	78	(Kunwar near3 SHAILUBHAI).in.	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42
S24	0	(SYNERGY near3 PHARMACEUTICALS).in.	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42
S25	207	S20 or S21 or S22 or S23	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42
S26	0	S25 and S17	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42
S27	10	S25 and S18	US-PGPUB; USPAT	WITH	ON	2017/12/19 13:42

12/19/2017 2:09:08 PM
C:\Users\jlee24\Documents\EAST\Workspaces\15 467648.wsp

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

58249 7590 01/08/2018
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DISTRICT OF COLUMBIA 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/467,648	03/23/2017	Stephen COMISKEY	SYPA-009C04US 321994-2341	2133

TITLE OF INVENTION: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
REGULAR	SMALL	$480	$0.00	$0.00	$480	04/09/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEE, JIA-HAI	1676	424-451000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Cynthia A. Kozakiewicz
2 Ivor Elrifi
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: SYNERGY PHARMACEUTICALS, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): NEW YORK, NEW YORK

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ● Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

● Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

● The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 50-1283 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Anne E Fleckenstein/ Date January 31, 2018

Typed or printed name Anne E. Fleckenstein Registration No. 62,951

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal

Application Number:	15467648
Filing Date:	23-Mar-2017
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Filer:	Anne Elizabeth Fleckenstein/virginia melton
Attorney Docket Number:	SYPA-009C04US 321994-2341

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	480	480

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**480**

Electronic Acknowledgement Receipt

EFS ID:	31663206
Application Number:	15467648
International Application Number:	
Confirmation Number:	2133
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009C04US 321994-2341
Receipt Date:	31-JAN-2018
Filing Date:	23-MAR-2017
Time Stamp:	16:59:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$480
RAM confirmation Number	020118INTEFSW00003927501283
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	SYPA-009_C04US_IF_Transmittal.pdf	116194 3de6272c15dc47b3e43be1bf9fef075acc762ca7	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30830 19587f6081f12dcf409c0250932cc345c8164d54	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	147024		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Notice of References Cited	Application/Control No. 15/467,648	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-9,610,321 B2	04-2017	Comiskey; Stephen	A61K9/1623	1/1
*	B	US-9,616,097 B2	04-2017	Comiskey; Stephen	A61K9/1623	1/1
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

Change(s) applied to document, /K.M./ 8/28/2017

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO2008151257A2	12-2008	~~US~~ WO	Shailubhai et al.	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Shailubhai, K.; Gerson, W.; Talluto, C.; Jacob, G. Digestive Disease Week. San Diego: 2008. A randomized, double-blind, placebo-controlled, single-, ascending-, oral-dose safety, tolerability and pharmacokinetic study of SP-304 in healthy adult human male and female volunteers.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PTO/SB/08a (07-09)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 19

Complete if Known	
Application Number	15/467,648
Filing Date	March 23, 2017
First Named Inventor	COMISKEY, Stephen
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C04US 321994-2341

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/J.L/	30.	8,716,224	05-06-2014	Shailubhai et al.	
/J.L/	31.	8,901,075	12-02-2014	Shailubhai et al.	
/J.L/	32.	8,969,514	03-03-2015	Shailubhai	
/J.L/	33.	9,238,677	01-19-2016	Shailubhai et al.	
/J.L/	34.	9,266,926	02-23-2016	Shailubhai et al.	
/J.L/	35.	9,486,494	11-08-2016	Shailubhai	
/J.L/	36.	9,545,446 01/2017	~~01-17-2016~~	Riff et al.	
/J.L/	37.	2002/0128176 A1	09-12-2002	Forssmann et al.	
/J.L/	38.	2002/0133168 A1	09-19-2002	Smeldley et al.	
/J.L/	39.	2002/0143015 A1	10-03-2002	Fryburg et al.	
/J.L/	40.	2003/0073628 A1	04-17-2003	Shailubhai et al.	
/J.L/	41.	2004/0015140 A1	01-22-2004	Shields	
/J.L/	42.	2005/0016244 A1	01-27-2005	Hergemoller	
/J.L/	43.	2005/0032684 A1	02-10-2005	Cetin et al.	
/J.L/	44.	2005/0107734 A1	05-19-2005	Coroneo	
/J.L/	45.	2005/0145351 A1	07-07-2005	Schaible, et al.	
/J.L/	46.	2005/0266047 A1	12-01-2005	Tu et al	
/J.L/	47.	2005/0267297 A1	12-01-2005	Berlin	
/J.L/	48.	2006/0086653 A1	04-27-2006	St. Germain	
/J.L/	49.	2006/0094658 A1	05-04-2006	Currie	
/J.L/	50.	2007/0101158 A1	05-03-2007	Elliott	
/J.L/	51.	2008/0137318 A1	06-12-2008	Rangaraj et al.	
/J.L/	52.	2008/0151257 A1	06-26-2008	Yasuda et al.	
/J.L/	53.	2009/0048175 A1	02-19-2009	Shailubhai et al.	
/J.L/	54.	2009/0192083 A1	07-30-2009	Currie	
/J.L/	55.	2009/0253634 A1	10-08-2009	Currie et al.	
/J.L/	56.	2010/0048489 A1	02-25-2010	Fretzen	
/J.L/	57.	2010/0069306 A1	03-18-2010	Shailubhai et al.	
/J.L/	58.	2010/0093635 A1	04-15-2010	Shailubhai	

Change(s) applied to document. /J.H/ 2/20/2018

Examiner Signature	/JIA-HAI LEE/	Date Considered	12/19/2017

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/467,648	03/20/2018	9919024	SYPA-009C04US 321994-2341	2133

58249 7590 02/28/2018

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Stephen COMISKEY, Doylestown, PA;
SYNERGY PHARMACEUTICALS, INC., New York, NY
Rong FENG, Langhorne, PA;
John FOSS, Doylestown, PA;
Kunwar SHAILUBHAI, Audubon, PA;

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
2:21–cv–10057–SRC–JSA	4/26/2021	NEWARK, NJ
PLAINTIFF BAUSCH HEALTH IRELAND LIMITED		DEFENDANT MSN LABORATORIES PRIVATE LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 9,919,024 B2	Mar. 20, 2018	SYNERGY PHARMACEUTICALS, INC.
2 US 9,925,231 B2	Mar. 27, 2018	SYNERGY PHARMACEUTICALS, INC.
3 US 10,011,637 B2	Jul. 3, 2018	SYNERGY PHARMACEUTICALS, INC.
4		
5		

In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Leroy Dunbar	4/26/2021

Copy 1––Upon initiation of action, mail this copy to Director Copy 3––Upon termination of action, mail this copy to Director
Copy 2––Upon filing document adding patent(s), mail this copy to Director Copy 4––Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
21-611-LPS	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,041,786	5/9/2006	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
2	7,799,897	9/21/2010	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
3	8,637,451	1/28/2014	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
4	9,610,321	4/4/2017	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
5	9,616,097	4/11/2017	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.

In the above---entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
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5		

In the above---entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Notice of Voluntary Dismissal

CLERK	(BY) DEPUTY CLERK	DATE
John A Cerino		5-6-2021

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

Page 2 of 2

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
21-611-LPS	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,919,024	3/20/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
2	9,925,231	3/27/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
3	10,011,637	7/3/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
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3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAUSCH HEALTH IRELAND LIMITED, and SALIX PHARMACEUTICALS, INC. Plaintiffs, v. MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. — a VIATRIS COMPANY, Defendants.	C.A. No. 1:21-cv-00611-LPS

NOTICE OF VOLUNTARY DISMISSAL WITHOUT PREJUDICE

Plaintiffs Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc., pursuant to Fed. R. Civ. P. 41(a)(1)(A)(i), hereby voluntarily dismiss this action, without prejudice.

GIBBONS P.C.

By: */s/ Christopher Viceconte*
Christopher Viceconte (No. 5568)
Jennifer M. Rutter (No. 6200)
300 Delaware Avenue, Suite 1015
Wilmington, Delaware 19801
Tel: (302) 518-6322
Fax: (302) 397-2050
cviceconte@gibbonslaw.com
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Attorneys for Plaintiffs Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.

OF COUNSEL:

Bryan C. Diner
Justin J. Hasford
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
901 New York Avenue, NW
Washington, DC 20001-4413
Tel: (202) 408-4000

Dated: May 5, 2021

PTO/AIA/81A (02-15)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	9,919,024
Issue Date	March 20, 2018
First Named Inventor	Stephen Comiskey
Title	Formulations of Guanylate Cyclase C Agonists and Methods of Use
Attorney Docket No.	376464-2005US5 (00112)

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the Customer Number identified in the box at right as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 162421

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-identified Customer Number.

OR

☐ The address associated with the Customer Number identified in the box at right:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(c) (Form PTO/AIA/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Patent Owner

Signature		Date	August 22, 2018
Name	Robert Caldwell	Telephone	
Title and Company	VP and Assistant General Counsel, IP, Bausch Health Ireland Limited		

NOTE: Signatures of all the applicants or patent owners of the entire interest or their representative(s) are required. If more than one signature is required, submit multiple forms, check the box below, and identify the total number of forms submitted in the blank below.

☐ A total of _____ forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Synergy Pharmaceuticals Inc.

Application No./Patent No.: 15/467,648 / 9,919,024 Filed/Issue Date: March 23, 2017 / March 20, 2018

Titled: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

Bausch Health Ireland Limited, a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: S Comiskey, R Feng, J Foss, K Shailubhai To: Synergy Pharmaceuticals Inc.

   The document was recorded in the United States Patent and Trademark Office at
   Reel 041833, Frame 0927, or for which a copy thereof is attached.

2. From: Synergy Pharmaceuticals Inc. To: Bausch Health Ireland Limited

   The document was recorded in the United States Patent and Trademark Office at
   Reel 056706, Frame 0105, or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

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5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

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6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Domingos J. Silva/	August 24, 2021
Signature	Date
Domingos J. Silva	64197
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	43587069
Application Number:	15467648
International Application Number:	
Confirmation Number:	2133
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Domingos J. Silva/Catherine Rose
Filer Authorized By:	Domingos J. Silva
Attorney Docket Number:	SYPA-009C04US 321994-2341
Receipt Date:	24-AUG-2021
Filing Date:	23-MAR-2017
Time Stamp:	13:58:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	376464-2005US5_POA.pdf	240832 0ef516dedce9e4b2608d7ccf117047343376 9771	no	2

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	376464-2005US5_Statement_373c.pdf	3852679 e906becbe7e708eee9431f91d500abda72484028	no	3
Warnings:					
Information:					
			Total Files Size (in bytes):	4093511	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
15/467,648	03/23/2017	Stephen COMISKEY	376464-2005US5 (00112)	146408

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 08/26/2021 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

X Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Domingos J. Silva/
Name:	DOMINGOS J. SILVA
Registration Number:	64197

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/467,648	03/23/2017	Stephen COMISKEY	376464-2005US5 (00112)

CONFIRMATION NO. 2133

POA ACCEPTANCE LETTER

162421
SAUL EWING ARNSTEIN & LEHR LLP (Bausch Health)
Attn: Patent Docket Clerk, Centre Square West,
1500 Market Street, 38th Floor
Philadelphia, PA 19102-2186

OC00000128020762

Date Mailed: 08/27/2021

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/24/2021.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/tlulu/

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UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/467,648	03/23/2017	Stephen COMISKEY	SYPA-009C04US 321994-2341

CONFIRMATION NO. 2133

POWER OF ATTORNEY NOTICE

58249
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

OC000000128020742

Date Mailed: 08/27/2021

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/24/2021.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/tlulu/