IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Bruce Scharschmidt et al.
Title:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
Appl. No.:	To be assigned
Filing Date:	Herewith
Examiner:	To be assigned
Art Unit:	To be assigned
Confirmation Number:	To be assigned

PRELIMINARY AMENDMENT UNDER 37 CFR 1.115

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Prior to examination, please amend the application as indicated on the following pages.

This paper contains:

Amendments to the Specification are reflected on page 2 of this document.

Amendments to the Drawings are reflected on page 3 of this document.

Amendments to the Claims are reflected on page 4 of this document.

Remarks/Arguments follow the Amendments to the Claims.

Please amend the application as follows:

Amendments to the Specification:

Please amend paragraph [001] as follows:

[0001] The present application is a continuation of U.S. Patent Application 14/816,674, filed August 3, 2015, which is a continuation of U.S. Patent Application 13/775,000, filed February 22, 2013 and now issued as U.S. Patent 9,095,559, which is a continuation ~~divisional~~ of U.S. Patent Application No. 13/417,137, filed March 9, 2012, ~~and now pending~~ issued as U.S. Patent 8,404,215, which claims the benefit of U.S. Provisional Application No. 61/564,668, filed November 29, 2011, and U.S. Provisional Application No. 61/542,100, filed September 30, 2011, the disclosures of which are incorporated by reference herein in their entirety, including drawings.

Amendments to the Drawings:

Please replace Figures 1-3 with the accompanying replacement formal drawing sheets for Figures 1-3.

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1.-11. (Cancelled)

12. (New) A method of treating a subject with a urea cycle disorder, the method comprising:

administering to the subject in need thereof glyceryl tri-[4-phenylbutyrate] in an amount sufficient to produce a fasting plasma ammonia level that is less than half the upper limit of normal for plasma ammonia level,

wherein the method further comprises restricting the subject's dietary protein intake.

13. (New) The method of claim 12, wherein the upper limit of normal for plasma ammonia level is 35 μmol/L.

14. (New) The method of claim 12, wherein the glyceryl tri-[4-phenylbutyrate] is administered orally.

15. (New) A method of treating a subject with a urea cycle disorder, the method comprising:

administering to the subject in need thereof glyceryl tri-[4-phenylbutyrate] in an amount sufficient to produce a fasting plasma ammonia level that is less than half the upper limit of normal for plasma ammonia level,

wherein the method further comprises monitoring the subject's ammonia levels if the glyceryl tri-[4-phenylbutyrate] is not being adequately digested by the subject's pancreatic lipases.

16. (New) The method of claim 15, wherein the glyceryl tri-[4-phenylbutyrate] is administered orally.

17. (New) A method for adjusting the dosage of glyceryl tri-[4-phenylbutyrate] in a subject being treated for a urea cycle disorder who has previously been administered an initial dosage of sodium phenylbutyrate, the method comprising:

administering an initial dosage of glyceryl tri-[4-phenylbutyrate], wherein the initial dosage is determined by the amount of the initial dosage of sodium phenylbutyrate, and

administering to the subject in need thereof an adjusted dosage of glyceryl tri-[4-phenylbutyrate], wherein the adjusted dosage of glyceryl tri-[4-phenylbutyrate] is an amount sufficient to produce a fasting plasma ammonia level that is less than half the upper limit of normal for plasma ammonia level.

18. (New) The method of claim 17, wherein the initial dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

19. (New) The method of claim 17, wherein the adjusted dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

20. (New) A method of treating a pediatric subject with a urea cycle disorder, the method comprising:

administering to the pediatric subject glyceryl tri-[4-phenylbutyrate] in an amount sufficient to produce a fasting plasma ammonia level that is less than half the upper limit of normal for plasma ammonia level,

wherein said administration results in an improvement in executive function in the pediatric subject.

21. (New) The method of claim 20, wherein the glyceryl tri-[4-phenylbutyrate] is administered orally.

REMARKS

Applicant respectfully requests that the foregoing amendments be made prior to examination of the present application. In the specification, the priority paragraph has been added. In addition, the figures have been replaced with formal drawing sheets. Finally, claims 1-11 have been cancelled without prejudice or disclaimer. Claims 12-21 have been added. No new matter has been introduced by those amendments.

Applicant believes that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone or email, if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

By /Lauren L. STEVENS/

Lauren L. Stevens
Attorney for Applicant
Registration No. 36,691
lstevens@globalpatentgroup.com

Figure 1

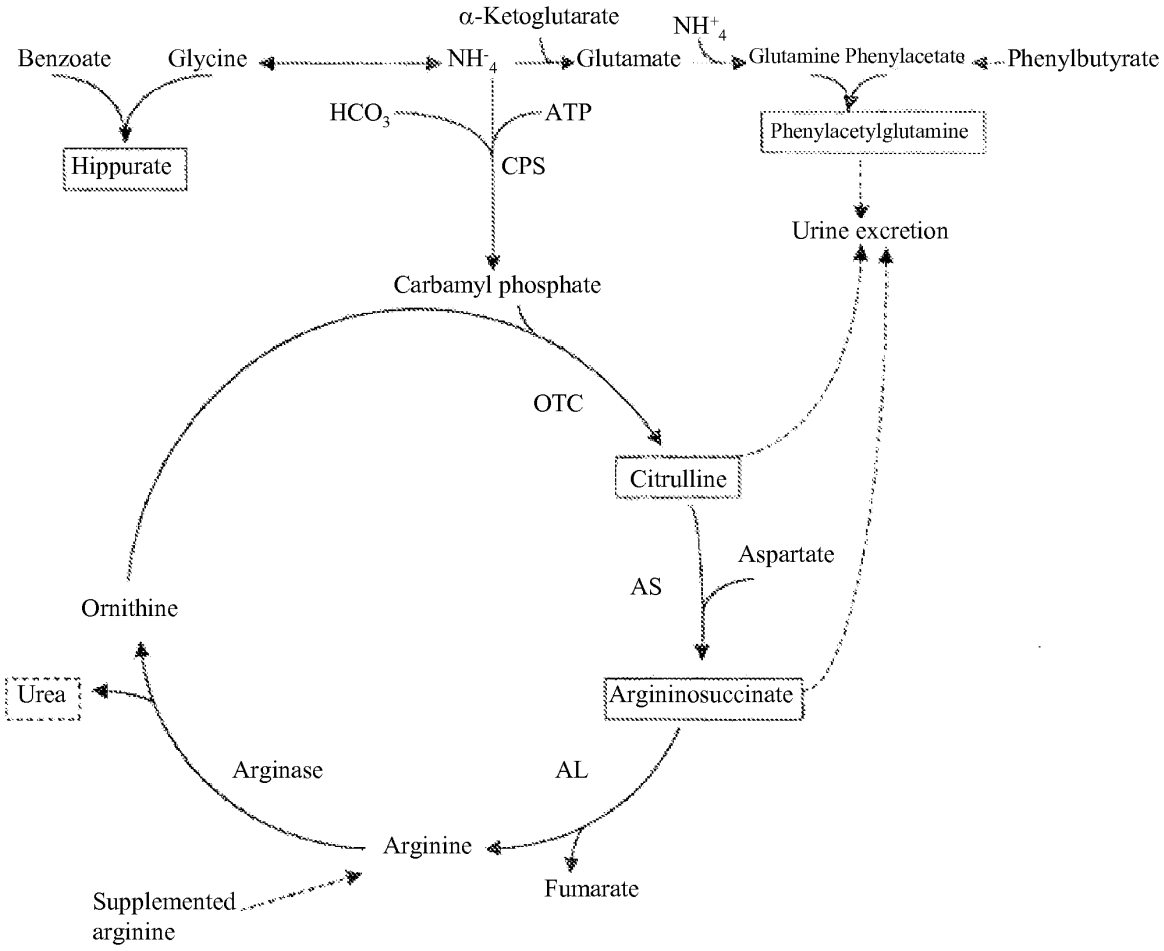

α-Ketoglutarate
NH^+_4
Benzoate
Glycine
NH^-_4
Glutamate
Glutamine
Phenylacetate
Phenylbutyrate
HCO_3
ATP
Phenylacetylglutamine
Hippurate
CPS
Urine excretion
Carbamyl phosphate
OTC
Citrulline
Aspartate
AS
Ornithine
Urea
Argininosuccinate
Arginase
AL
Arginine
Fumarate
Supplemented arginine

Figure 2

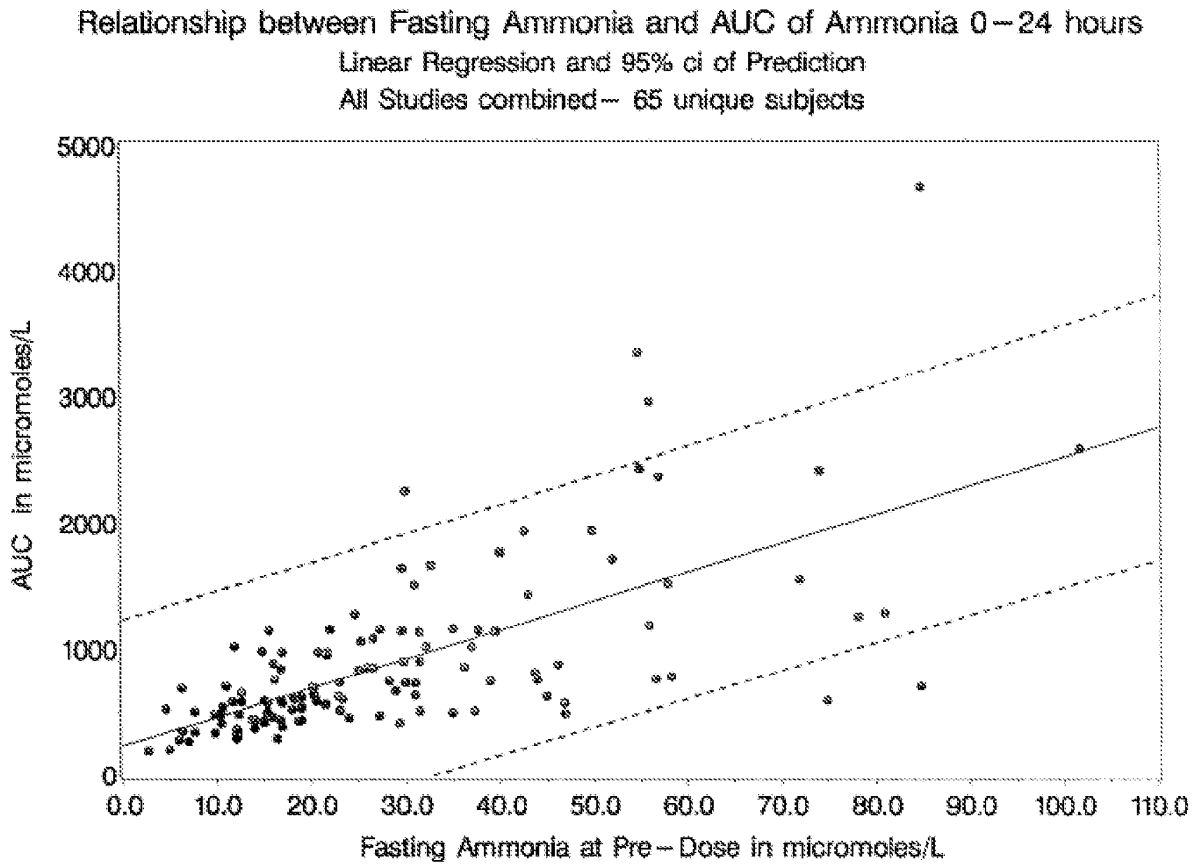
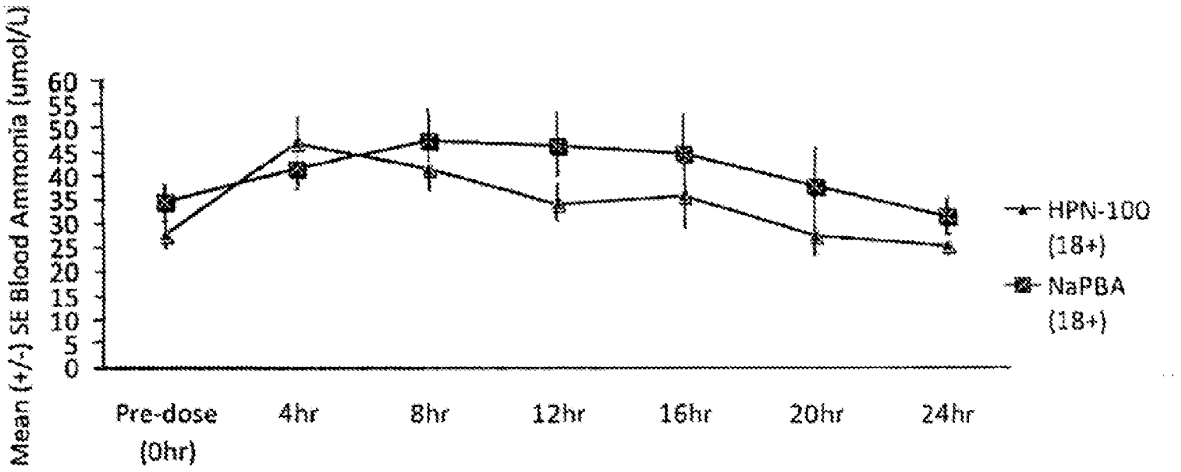
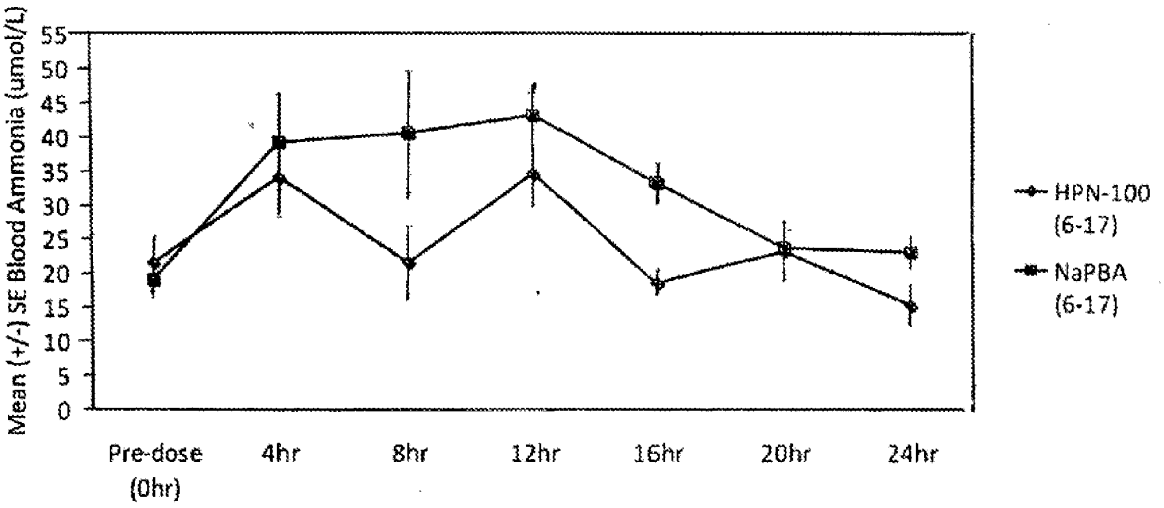

Relationship between Fasting Ammonia and AUC of Ammonia 0 – 24 hours
Linear Regression and 95% ci of Prediction
All Studies combined – 65 unique subjects
AUC in micromoles/L
5000
4000
3000
2000
1000
0
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
Fasting Ammonia at Pre – Dose in micromoles/L

Figure 3

A.


Mean (+/-) SE Blood Ammonia (umol/L)
60
55
50
45
40
35
30
25
20
15
10
5
0
Pre-dose (0hr)
4hr
8hr
12hr
16hr
20hr
24hr
HPN-100 (18+)
NaPBA (18+)

B.


Mean (+/-) SE Blood Ammonia (umol/L)
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50
45
40
35
30
25
20
15
10
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Pre-dose (0hr)
4hr
8hr
12hr
16hr
20hr
24hr
HPN-100 (6-17)
NaPBA (6-17)

Attorney Docket No.: HOR0026-201TC2-US

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Scharschmidt et al.	)
			) Group Art Unit:
Serial No.	:	To be assigned	) To be assigned
			)
Filed	:	Herewith	)
			) Examiner:
			) To be assigned

Title: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.561

ELECTRONICALLY VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

Applicant requests that, in accordance with 37 CFR §1.98(d), the Examiner review all applications relied on for an earlier effective filing date under 35 U.S.C. 120, including application no. 14/816,674, filed August 3, 2015, application no. 13/775,000, filed February 22, 2013, now U.S. Patent 9,095,559, and application no. 13/417,137, filed March 9, 2012, now U.S. Patent 8,404,215, for copies of references of record therein that are not being provided here;

although Applicant would be pleased to provide copies of any such documents at the Examiner's request.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith. Authorization is hereby given to treat this and any future reply, which requires or might require a petition for an extension of time under 37 CFR § 1.136(a) for its timely submission or payment of fee, as incorporating a petition for extension of time for the appropriate length of time and an authorization to pay any required fees from Deposit Account No. 50-4297.

Respectfully submitted,

By /Lauren L. STEVENS/

Lauren L. Stevens
Attorney for Applicant
Registration No. 36,691
(650) 387-3813

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Scharschmidt	Nonprovisional Application Number (if known):	
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Lauren L. STEVENS/	Date 12-3-2015
Name (Print/Typed) Lauren L. Stevens	Practitioner Registration Number 36691

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *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.

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

Title of Invention	**METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 13/775,000 filed on February 22, 2013.

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 state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I am aware of and acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56.

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.

LEGAL NAME OF INVENTOR: **Masoud Mokhtarani**

Signature: _____ **Date:** 3/15/2013

Perkins Coie

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

Title of Invention	**METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS**

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☐ The attached application, or

☒ United States application or PCT international application number 13/775,000 filed on February 22, 2013.

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.

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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.

LEGAL NAME OF INVENTOR: **Bruce Scharschmidt**

Signature: Bruce F. Scharschmidt **Date:** 3/15/13

Perkins Coie

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

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

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.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 101325

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
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):

Horizon Therapeutics, 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	[signature]	Date (Optional)	5/1/15
Name	Bryan R. Beelen		
Title	SVP, Legal		

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.

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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Lauren Stevens/Vicki Truman
Attorney Docket Number:	HOR0026-201TC2-US

Filed as Large Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Independent claims in excess of 3	1201	1	420	420
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**6160**

Electronic Acknowledgement Receipt	
EFS ID:	24255987
Application Number:	14958259
International Application Number:	
Confirmation Number:	3046
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Lauren Stevens/Vicki Truman
Filer Authorized By:	Lauren Stevens
Attorney Docket Number:	HOR0026-201TC2-US
Receipt Date:	03-DEC-2015
Filing Date:	
Time Stamp:	15:52:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$6160
RAM confirmation Number	2397
Deposit Account	504297
Authorized User	BENNETT, DENNIS A.
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	20151203_ADS.pdf	1819419 dc7a23d1c02d00127f4e2eb322b611cac3e23ea1	no	7
Warnings:					
Information:					
2		20150803_Application.pdf	402212 359f789338e8b148193488d0084a2a451c1b3ca0	yes	38

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	32
	Claims	33	34
	Abstract	35	35
	Drawings-only black and white line drawings	36	38

Warnings:					
Information:					
3		20151203_Preliminary_Amendment.pdf	39479 53fd378a51373bca845c60df09ee47b7aadbabf6	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Specification	2	2
	Drawings-only black and white line drawings	3	3
	Claims	4	6
	Applicant Arguments/Remarks Made in an Amendment	7	7

Warnings:					
Information:					
4	Drawings-only black and white line drawings	20151203_Replacement_Drawings.pdf	232781 3758b55e524cbccad3058b4c0d977f854fdf05fc	no	3
Warnings:					
Information:					
5	Transmittal Letter	20151203_IDS_Trans.pdf	19803 945e24ec6e8d5035af4c04725437098188eb936f	no	2
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Form (SB08)	20151203_IDS.pdf	291681 3dfcfca9988f10a6200dffee6382a80356a99109	no	21
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
7	Internet Communications Authorized	20151203_Internet_Communication_Authorization.pdf	74953 ce00537b44432f7ea3c89792086cef2d61fd52b7	no	2
Warnings:					
Information:					
8	Miscellaneous Incoming Letter	20151203_Notice_Related_Litigation.pdf	20958 b6e412ae057f4a8c307607653aa45df39906532c	no	2
Warnings:					
Information:					
9	Non Patent Literature	Xie_G_2012_Gastroenterology_142_918-927_124110051_1.PDF	6518066 3257c9a1c2831745b17a551bed9a2f6a2512081a	no	16
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Information:					
10	Non Patent Literature	20151106_Lupin_Second_Notice_Letter_559.pdf	1629327 b4f5324a30ae330ba548ad31b6a3ecfc98ca751a	no	30
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Information:					
11	TrackOne Request	20151203_Track_1.pdf	113876 ddf3c5045897fc63eda016192a2f4da8abb69688	no	2
Warnings:					
Information:					

12	Oath or Declaration filed	20151203_Declaration.pdf	156713 c2a093eea2c007ed4bb62903448844bc1ff49705	no	2
Warnings:					
Information:					
13	Power of Attorney	Horizon_Therapeutics_Applicant.pdf	106357 f674dfc6ed140e4b2710f2e8e0c1dae0af853ed0	no	1
Warnings:					
Information:					
14	Fee Worksheet (SB06)	fee-info.pdf	41998 6a94182274680dbed8778f90bcc69f4e771ad9c1	no	2
Warnings:					
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			Total Files Size (in bytes):	11467623	

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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.

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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	HOR0026-201TC2-US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

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.)

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Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bruce		Scharschmidt	

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

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Inventor 2 Remove

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For further information see 37 CFR 1.33(a).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HOR0026-201TC2-US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

☐ **An Address is being provided for the correspondence Information of this application.**			
Customer Number	101325		
Email Address	admin@globalpatentgroup.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS		
Attorney Docket Number	HOR0026-201TC2-US	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	3	**Suggested Figure for Publication (if any)**	

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

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☐ **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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HOR0026-201TC2-US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

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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 this 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 blank.

Prior Application Status	Pending				Remove
Application Number	Continuity Type		Prior Application Number		Filing Date (YYYY-MM-DD)
	Continuation of		14/816674		2015-08-03
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/816674	Continuation of	13/775000	2013-02-22	9095559	2014-08-04
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/775000	Division of	13/417137	2012-03-09	8404215	2013-03-26
Prior Application Status	Expired				Remove
Application Number	Continuity Type		Prior Application Number		Filing Date (YYYY-MM-DD)
13/417137	Claims benefit of provisional		61/542100		2011-09-30
Prior Application Status	Expired				Remove
Application Number	Continuity Type		Prior Application Number		Filing Date (YYYY-MM-DD)
13/417137	Claims benefit of provisional		61/564668		2011-11-29

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HOR0026-201TC2-US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

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.

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☒ Authorization to Permit Access to the Instant Application by the Participating Offices

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Applicant Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HOR0026-201TC2-US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

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	

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Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	Horizon Therapeutics, Inc.

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Phone Number		Fax Number	
Email Address			

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HOR0026-201TC2-US
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Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

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

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Signature	/Lauren L. STEVENS/			Date (YYYY-MM-DD)	2015-12-02
First Name	Lauren	Last Name	Stevens	Registration Number	36691

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METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

RELATED APPLICATIONS

[0001] The present application is a divisional of U.S. Patent Application No. 13/417,137, filed March 9, 2012 and now pending, which claims the benefit of U.S. Provisional Application No. 61/564,668, filed November 29, 2011, and U.S. Provisional Application No. 61/542,100, filed September 30, 2011, the disclosures of which are incorporated by reference herein in their entirety, including drawings.

BACKGROUND

[0002] Nitrogen retention disorders associated with elevated ammonia levels include urea cycle disorders (UCDs) and hepatic encephalopathy (HE).

[0003] UCDs include several inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia, including enzymes involved in the urea cycle. The urea cycle is depicted in Figure 1, which also illustrates how certain ammonia-scavenging drugs act to assist in elimination of excessive ammonia. With reference to Figure 1, N-acetyl glutamine synthetase (NAGS)-derived *N*-acetylglutamate binds to carbamyl phosphate synthetase (CPS), which activates CPS and results in the conversion of ammonia and bicarbonate to carbamyl phosphate. In turn, carbamyl phosphate reacts with ornithine to produce citrulline in a reaction mediated by ornithine transcarbamylase (OTC). A second molecule of waste nitrogen is incorporated into the urea cycle in the next reaction, mediated by arginosuccinate synthetase (ASS), in which citrulline is condensed with aspartic acid to form argininosuccinic acid. Argininosuccinic acid is cleaved by argininosuccinic lyase (ASL) to produce arginine and fumarate. In the final reaction of the urea cycle, arginase (ARG) cleaves arginine to produce ornithine and urea. Of the two atoms of nitrogen incorporated into urea, one originates from free ammonia (NH_4^+) and the other from aspartate. UCD individuals born with no meaningful residual urea synthetic capacity typically present in the first few days of life (neonatal presentation). Individuals with residual function typically present later in childhood or even in adulthood, and symptoms may be precipitated by increased dietary protein or physiological stress (e.g., intercurrent illness).

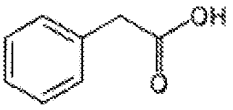
[0004] Hepatic encephalopathy (HE) refers to a spectrum of neurologic signs and symptoms believed to result from hyperammonemia, which frequently occur in subjects with cirrhosis or

certain other types of liver disease. Subjects with HE typically show altered mental status ranging from subtle changes to coma, features similar to subjects with UCDs.

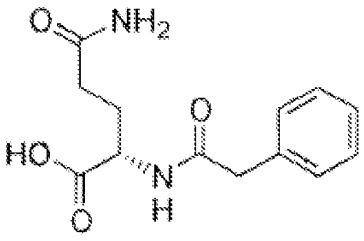
[0005] Subjects with nitrogen retention disorders whose ammonia levels and/or symptoms are not adequately controlled by dietary restriction of protein and/or dietary supplements are generally treated with nitrogen scavenging agents such as sodium phenylbutyrate (NaPBA, approved in the United States as BUPHENYL® and in Europe as AMMONAPS®) or sodium benzoate. These are often referred to as alternate pathway drugs because they provide the body with an alternate pathway to urea for excretion of waste nitrogen (Brusilow 1980; Brusilow 1991). NaPBA is a phenylacetic acid (PAA) prodrug. Another nitrogen scavenging drug currently in development for the treatment of nitrogen retention disorders is glyceryl tri-[4-phenylbutyrate](HPN-100), which is described in U.S. Patent No. 5,968,979. HPN-100, which is commonly referred to as GT4P or glycerol PBA, is a prodrug of PBA and a pre-prodrug of PAA.

[0006] HPN-100 and NaPBA share the same general mechanism of action: PBA is converted to PAA via beta oxidation, and PAA is conjugated enzymatically with glutamine to form phenylacetylglutamine (PAGN), which is excreted in the urine. The structures of PBA, PAA, and PAGN are set forth below.

phenylbutyrate



Phenylacetic acid



Phenylacetylglutamine

[0007] The clinical benefit of NaPBA and HPN-100 with regard to nitrogen retention disorders derives from the ability of PAGN to effectively replace urea as a vehicle for waste nitrogen excretion and/or to reduce the need for urea synthesis (Brusilow 1991; Brusilow 1993). Because

each glutamine contains two molecules of nitrogen, the body rids itself of two waste nitrogen atoms for every molecule of PAGN excreted in the urine. Therefore, two equivalents of nitrogen are removed for each mole of PAA converted to PAGN. PAGN represents the predominant terminal metabolite, and one that is stoichiometrically related to waste nitrogen removal, a measure of efficacy in the case of nitrogen retention states. The difference between HPN-100 and NaPBA with respect to metabolism is that HPN-100 is a triglyceride and requires digestion, presumably by pancreatic lipases, to release PBA (McGuire 2010).

[0008] In contrast to NaPBA or HPN-100, sodium benzoate acts when benzoic acid is combined enzymatically with glycine to form hippuric acid. For each molecule of hippuric acid excreted in the urine, the body rids itself of one waste nitrogen atom.

[0009] Methods of determining an effective dosage of PAA prodrugs such as NaPBA or HPN-100 for a subject in need of treatment for a nitrogen retention disorder are described in WO09/1134460 and WO10/025303. Daily ammonia levels, however, may vary greatly in a subject. This can lead to overestimation by the physician of the average daily ammonia levels, which may result in overtreatment. Thus, there is a need in the art for improved methods for PAA prodrug dose determination and adjustment based on ammonia levels in subjects with nitrogen retention disorders such as UCDs or HE.

SUMMARY

[0010] Provided herein in certain embodiments are methods for determining whether to increase a dosage of a nitrogen scavenging drug in a subject with a nitrogen retention disorder by measuring a fasting blood ammonia level and comparing the fasting blood ammonia level to the upper limit of normal (ULN) for blood ammonia, where a fasting blood ammonia level that is greater than half the ULN for blood ammonia indicates that the dosage needs to be increased. In certain embodiments, the nitrogen retention disorder is a UCD or HE. In certain embodiments, the nitrogen scavenging drug is HPN-100, PBA, NaPBA, sodium benzoate, or any combination thereof (i.e., any combination of two or more of HPN-100, PBA, NaPBA). In certain embodiments, the ULN is around 35 μmol/L or 59 μg/mL. In certain embodiments, the methods include an additional step of administering an increased dosage of the nitrogen scavenging drug if the need exists, and in certain of these embodiments administration of the nitrogen scavenging drug produces a normal average daily ammonia level in the subject. In certain embodiments wherein a determination is made to administer an increased dosage of nitrogen scavenging drug

and wherein the nitrogen scavenging drug is a PAA prodrug, the methods include an additional step of measuring urinary PAGN excretion and determining an effective dosage of the PAA prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60-75%.

[0011] Provided herein in certain embodiments are methods for determining whether to administer a nitrogen scavenging drug to a subject with a nitrogen retention disorder by measuring a fasting blood ammonia level and comparing the fasting blood ammonia level to the ULN for blood ammonia, where a fasting blood ammonia level that is greater than half the ULN for blood ammonia indicates that the nitrogen scavenging drug needs to be administered. In certain embodiments, the nitrogen retention disorder is a UCD or HE. In certain embodiments, the nitrogen scavenging drug is HPN-100, PBA, NaPBA, sodium benzoate, or any combination thereof (i.e., any combination of two or more of HPN-100, PBA, NaPBA). In certain embodiments, the ULN is around 35 μmol/L or 59 μg/mL. In certain embodiments, the methods include an additional step of administering a nitrogen scavenging drug if the need exists, and in certain of these embodiments administration of the nitrogen scavenging drug produces a normal average daily ammonia level in the subject. In certain embodiments wherein a determination is made to administer a nitrogen scavenging drug and wherein the nitrogen scavenging drug is a PAA prodrug, the methods further include a step of determining an effective initial dosage of the PAA prodrug by determining a target urinary PAGN output based on a target nitrogen output and calculating an effective initial dosage that results in the target urinary PAGN output based on a mean conversion of PAA prodrug to urinary PAGN of 60-75%. In certain embodiments, the methods include a step of administering the calculated effective initial dosage.

[0012] Provided herein in certain embodiments are methods for treating a nitrogen retention disorder in a subject who has previously been administered a nitrogen scavenging drug by measuring a fasting blood ammonia level, comparing the fasting blood ammonia level to the ULN for blood ammonia, and administering an increased dosage of the nitrogen scavenging drug if the fasting ammonia level is greater than half the ULN for blood ammonia. In certain embodiments, administration of an increased dosage of the nitrogen scavenging drug produces a normal average daily ammonia level in the subject. In certain embodiments, the nitrogen retention disorder is a UCD or HE. In certain embodiments, the nitrogen scavenging drug is HPN-100, PBA, NaPBA, sodium benzoate, or any combination thereof (i.e., any combination of two or more of HPN-100, PBA, NaPBA). In certain embodiments, the ULN is around 35

μmol/L or 59 μg/mL. In certain embodiments wherein the nitrogen scavenging drug is a PAA prodrug, the methods include an additional step of measuring urinary PAGN excretion and determining an effective dosage of the PAA prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60-75%. In certain embodiments, the methods include a step of administering the calculated effective dosage.

BRIEF DESCRIPTION OF DRAWINGS

[0013] Figure 1: The urea cycle and how certain nitrogen-scavenging drugs may assist in elimination of excessive ammonia.

[0014] Figure 2: Relationship between fasting ammonia and average ammonia UCD patients.

[0015] Figure 3: Venous blood ammonia values over 24 hours in (A) adult and (B) pediatric UCD patients.

DETAILED DESCRIPTION

[0016] The following description of the invention is merely intended to illustrate various embodiments of the invention. As such, the specific modifications discussed are not to be construed as limitations on the scope of the invention. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of the invention, and it is understood that such equivalent embodiments are to be included herein.

[0017] In subjects with a nitrogen retention disorder, the desired effect of treatment with a nitrogen scavenging drug is control of blood ammonia level. Control of blood ammonia level generally refers to ammonia values within the normal range and avoidance of hyperammonemic crises, which are often defined in the art as transient ammonia values exceeding 100 μmol/L or 178 μg/mL accompanied by clinical signs and symptoms of hyperammonemia. Dosing of nitrogen scavenging drugs is usually based upon clinical assessment and measurement of ammonia. However, assessment of treatment effect and interpretation of ammonia levels is confounded by the fact that individual ammonia values vary several-fold over the course of a day and are impacted by timing of the blood draw in relation to the last meal and dose of drug (see, e.g., Lee 2010; Lichter-Konecki 2011; Diaz 2011).

[0018] A random ammonia value obtained during an outpatient visit may fail to provide a reliable measure of a subject's status and the drug effect. For example, basing treatment on a blood sample taken after eating a meal might overestimate average daily ammonia level and

result in overtreatment. Conversely, basing treatment on a blood sample taken after drug administration might underestimate average daily ammonia level and result in undertreatment. A fasting ammonia level at or near the ULN might be taken as an indication of satisfactory control without appreciating the fact that the ammonia burden during the day (average and/or highest possible value) might be significantly higher. Thus, a fasting level at or near the ULN may actually reflect undertreatment in a subject already a receiving nitrogen scavenging drug or the need for treatment in a subject not currently prescribed a nitrogen scavenging drug. A more accurate view of daily ammonia level could be obtained by multiple blood draws in a controlled setting over an extended period of time. Although this is currently done in clinical trials, it is clinically impractical.

[0019] As set forth below, the relationship between fasting ammonia levels and daily ammonia exposure was evaluated in subjects with nitrogen retention disorders. It was found that fasting ammonia correlates strongly with daily ammonia exposure, assessed as a 24 hour area under the curve for ammonia, daily average, or maximal daily concentration, and that a target fasting value which does not exceed half of the ULN is a clinically useful and practical predictor of ammonia values over 24 hours. As such, provided herein are clinically practical methods of evaluating ammonia exposure in subjects with nitrogen retention disorders based on fasting ammonia levels, as well as methods of using the resultant information to adjust the dosage of a nitrogen scavenging drug, determine whether to administer a nitrogen scavenging drug, treat a nitrogen retention disorder, and predict daily ammonia burden. The use of fasting ammonia levels to predict ammonia exposure provides a significant advantage over previously developed methods by reducing the number of required blood draws and eliminating the confusion associated with conflicting ammonia levels over the course of the day.

[0020] As further disclosed herein, the relationship between ammonia control and neurocognitive outcome was evaluated in UCD patients. Previous research has demonstrated that UCD patients often exhibit lower IQ overall and deficient executive function manifested by difficulty in goal setting, planning, monitoring progress and purposeful problem solving. As set forth herein, it was found that ammonia control with GPB resulted in a significant improvement in executive functions in pediatric patients. Based on these results, methods are provided herein for improving executive function in a pediatric subject with a UCD by administering one or more nitrogen scavenging drugs.

[0021] As further disclosed herein, the relationship between elevated PAA levels and neurological adverse events (AEs) was analyzed. Many of the over 30 reports of administration of NaPBA and/or sodium PAA to humans describe AEs, particularly when administered intravenously. IV administration of PAA to cancer patients was shown previously to result in AEs that included fatigue, dizziness, dysgeusia, headache, somnolence, lightheadedness, pedal edema, nausea, vomiting, and rash (Thibault 1994; Thibault 1995). These AEs correlated with PAA levels from 499 to 1285 μg/mL. Although NaPBA has been used in UCD treatment for over two decades and AEs reportedly associated with PAA are similar to those associated with hyperammonemia, little was known previously about the relationship between PAA levels and neurological AEs in UCD patients. As shown herein, increased PAA levels did not correlate with increased neurological AEs in subjects with UCD. However, PAA levels were associated with an increase in neurological AEs in healthy subjects. Based on these results, methods are provided herein for predicting or diagnosing AEs in a subject by measuring PAA levels. Further provided herein are methods of treating and/or preventing AEs in a subject with elevated PAA levels by administering one or more nitrogen scavenging drugs.

[0022] Provided herein are specific target values for blood ammonia upon which an effective dosage of a nitrogen scavenging drug can be based. In certain embodiments, an effective dosage of a nitrogen scavenging drug may be an initial dosage, subsequent/maintenance dosage, improved dosage, or a dosage determined in combination with other factors. In certain embodiments, the effective dosage may be the same as or different than the initial dosage. In other embodiments, the effective dosage may be higher or lower than the initial dosage. In certain embodiments, methods are provided for adjusting the dose or regimen of a nitrogen scavenging drug to achieve a target ammonia level that is predictive of the average daily ammonia level and/or the highest ammonia value that the subject is likely to experience during the day.

[0023] Using the methods herein, a subject's fasting blood ammonia level may be used as a predictor of daily ammonia burden, average daily ammonia level, and/or highest daily ammonia value. Whether a subject with a nitrogen retention disorder is receiving an optimum dosage of nitrogen scavenging drug may be determined based on predicted daily ammonia exposure. By optimizing the therapeutic efficacy of a nitrogen scavenging drug, the therapeutic dosage of the nitrogen scavenging drug is adjusted so that the subject experiences the desired nitrogen

scavenging effect. In particular, the dose is adjusted so that the subject may experience a normal average daily ammonia level. In certain embodiments, the effective dosage of nitrogen scavenging drug is determined by adjusting (e.g., increasing) a dosage to achieve a fasting blood ammonia level for a subject that is less than or equal to half the ULN for blood ammonia.

[0024] Provided herein in certain embodiments are methods of determining whether the dosage of a nitrogen scavenging drug needs to be increased in a subject with a nitrogen retention disorder comprising comparing a fasting blood ammonia level for the subject to a ULN for blood ammonia. If the fasting blood ammonia level has a value that greater than half the ULN, the dosage of the nitrogen scavenging drug needs to be increased. In certain embodiments, the methods further comprise increasing the dosage of the nitrogen scavenging drug if the need exists, and in certain of these embodiments the methods further comprise administering the increased dosage. In certain of these embodiments, administration of the increased dosage results in a normal average daily ammonia level in the subject.

[0025] Provided herein in certain embodiments are methods of determining whether the dosage of a nitrogen scavenging drug needs to be increased in a subject with a nitrogen retention disorder comprising measuring a fasting blood ammonia level for the subject and comparing the fasting blood ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, the dosage of the nitrogen scavenging drug needs to be increased. In certain embodiments, the methods further comprise increasing the dosage of the nitrogen scavenging drug if the need exists, and in certain of these embodiments the methods further comprise administering the increased dosage. In certain of these embodiments, administration of the increased dosage results in a normal average daily ammonia level in the subject.

[0026] Provided herein in certain embodiments are methods of adjusting the dosage of a nitrogen scavenging drug in a subject with a nitrogen retention disorder comprising comparing a fasting blood ammonia level for the subject to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, the dosage of the nitrogen scavenging drug is increased, and if the dosage is less than or equal to half the ULN the dosage of the nitrogen scavenging drug is not increased. In certain embodiments, the methods further comprise administering the increased dosage. In certain of these embodiments, administration of the increased dosage results in a normal average daily ammonia level in the subject.

[0027] Provided herein in certain embodiments are methods of adjusting the dosage of a nitrogen scavenging drug in a subject with a nitrogen retention disorder comprising measuring a fasting blood ammonia level for the subject and comparing the fasting blood ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, the dosage of the nitrogen scavenging drug is increased, and if the dosage is less than or equal to half the ULN the dosage of the nitrogen scavenging drug is not increased. In certain embodiments, the methods further comprise administering the increased dosage. In certain of these embodiments, administration of the increased dosage results in a normal average daily ammonia level in the subject.

[0028] Provided herein in certain embodiments are methods of adjusting the dosage of a nitrogen scavenging drug in a subject with a nitrogen retention disorder comprising measuring a fasting blood ammonia level for the subject and comparing the fasting blood ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, the dosage of the nitrogen scavenging drug is increased, and if the dosage is significantly less than half the ULN, the dosage of the nitrogen scavenging drug may be decreased. In certain embodiments, the methods further comprise administering the adjusted dosage. In certain of these embodiments, administration of the adjusted dosage results in a normal average daily ammonia level in the subject.

[0029] Provided herein in certain embodiments are methods of adjusting the dosage of a nitrogen scavenging drug in a subject with a nitrogen retention disorder comprising administering an initial dosage of the nitrogen scavenging drug, measuring fasting blood ammonia level, and comparing the fasting blood ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, subsequent maintenance dosages of the nitrogen scavenging drug are adjusted to be greater than the initial dosage. In certain embodiments, the methods further comprise administering the increased maintenance dosage, and in certain of these embodiments, administration of the increased maintenance dosage results in a normal average daily ammonia level in the subject.

[0030] Provided herein in certain embodiments are methods of adjusting the dosage of a nitrogen scavenging drug in a subject with a nitrogen retention disorder to achieve a fasting blood ammonia level that is less than or equal to half the ULN for blood ammonia comprising measuring a fasting blood ammonia level for the subject and comparing the fasting blood

ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, the subject is administered an increased dosage of the nitrogen scavenging drug. After a time period sufficient for the drug to reach steady state (e.g., 48 hours, 48 to 72 hours, 72 hours to 1 week, 1 week to 2 weeks, greater than 2 weeks), fasting blood ammonia level is measured again and compared to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, the dosage of the nitrogen scavenging drug is increased. This process is repeated until a fasting blood ammonia level of less than or equal to half the ULN is obtained.

[0031] Provided herein in certain embodiments are methods for assessing whether a subject with a nitrogen retention disorder is more or less likely to need a dosage adjustment of a nitrogen scavenging drug comprising measuring a fasting blood ammonia level for the subject and comparing the fasting blood ammonia level to a ULN for blood ammonia, wherein a fasting blood ammonia level that is greater than half the value of ULN indicates that the subject is more likely to need a dosage adjustment and a fasting blood ammonia level less than or equal to half the value of ULN indicates that the subject is less likely to need a dosage adjustment.

[0032] Provided herein in certain embodiments are methods of determining whether to administer a nitrogen scavenging drug to a subject with nitrogen retention disorder comprising comparing a fasting blood ammonia level for the subject to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, a nitrogen scavenging drug needs to be administered to the subject. In certain embodiments, these methods further comprise administering the nitrogen scavenging drug. In certain embodiments, the subject may not have been administered any nitrogen scavenging drugs prior to the determination. In other embodiments, the subject may have previously been administered a nitrogen scavenging drug other than the one being evaluated. In these embodiments, the methods provided herein can be used to determine whether to administer a new nitrogen scavenging drug to a subject.

[0033] Provided herein in certain embodiments are methods of determining whether to administer a nitrogen scavenging drug to a subject with nitrogen retention disorder comprising measuring a fasting blood ammonia level for the subject and comparing the fasting blood ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, a nitrogen scavenging drug needs to be administered to the subject. In certain embodiments, these methods further comprise administering the nitrogen scavenging

drug. In certain embodiments, the subject may not have been administered any nitrogen scavenging drugs prior to the determination. In other embodiments, the subject may have previously been administered a nitrogen scavenging drug other than the one being evaluated. In these embodiments, the methods provided herein can be used to determine whether to administer a new nitrogen scavenging drug to a subject.

[0034] Provided herein in certain embodiments are methods for selecting a dosage of a nitrogen scavenging drug for treating a nitrogen retention disorder in a subject based on blood ammonia levels comprising selecting a dosage that results in a fasting blood ammonia level that is less than or equal to half the ULN for blood ammonia. In certain embodiments, selecting the effective dosage is further based on diet, endogenous waste nitrogen excretion capacity, or any combination thereof. In certain embodiments, the methods further comprise administering the selected dosage.

[0035] Provided herein in certain embodiments are methods of treating a subject with a nitrogen retention disorder who has previously been administered a nitrogen scavenging drug comprising measuring a fasting blood ammonia level for the subject and comparing the fasting blood ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, the subject is administered an increased dosage of the nitrogen scavenging drug. If the fasting blood ammonia level has a value that is less than or equal to half the ULN, the subject is administered the same dosage or a decreased dosage of the nitrogen scavenging drug. In certain embodiments, administration of an increased dosage results in a normal average daily ammonia level in the subject.

[0036] Provided herein in certain embodiments are methods of treating a subject with a nitrogen retention disorder who has previously been administered an initial dosage of a nitrogen scavenging drug comprising measuring a fasting blood ammonia level for the subject and comparing the fasting blood ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, the subject is administered a maintenance dosage that is greater than the initial dosage of the nitrogen scavenging drug. If the fasting blood ammonia level has a value that is less than or equal to half the ULN, the subject is administered the initial dosage or a lower dosage. In certain embodiments, administration of an increased maintenance dosage results in a normal average daily ammonia level in the subject.

[0037] Provided herein in certain embodiments are methods of treating a subject with a nitrogen retention disorder comprising administering a nitrogen scavenging drug, then measuring a fasting blood ammonia level for the subject at some point after drug administration and comparing the fasting blood ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, the subject is administered an increased dosage of the nitrogen scavenging drug. If the fasting blood ammonia level has a value that is less than or equal to half the ULN, the subject is administered the original or a lower dosage of the drug.

[0038] Provided herein in certain embodiments are methods of treating a subject with a nitrogen retention disorder comprising administering a first dosage of a nitrogen scavenging drug, measuring a fasting blood ammonia level for the subject, and comparing the fasting blood ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, a second dosage of a nitrogen scavenging drug that is greater than the first dosage is administered to the subject. A fasting ammonia blood level is measured again in the subject and compared to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, a third dosage of a nitrogen scavenging drug that is greater than the second dosage is administered to the subject. This process is repeated until the subject exhibits a fasting blood ammonia level with a value less than or equal to half the ULN.

[0039] Provided herein in certain embodiments are methods of monitoring the efficacy of nitrogen scavenging drug administration in a subject with a nitrogen retention disorder who has previously been administered a nitrogen scavenging drug comprising measuring a fasting blood ammonia level for the subject and comparing the fasting blood ammonia level to a ULN for blood ammonia. If the fasting blood ammonia level has a value that is greater than half the ULN, the previously administered dosage of the nitrogen scavenging drug is considered inadequate to treat the nitrogen retention disorder. If the fasting blood ammonia level has a value that is less than or equal to half the ULN, the previously administered dosage is considered adequate to treat the nitrogen retention disorder. In certain embodiments where the previously administered dosage is considered inadequate to treat the nitrogen retention disorder, the methods provided herein further comprise administering an increased dosage of the nitrogen scavenging drug.

[0040] Provided herein in certain embodiments are methods for monitoring therapy with a nitrogen scavenging drug in a subject having a nitrogen retention disorder comprising measuring

a fasting blood ammonia level from the subject and comparing the fasting blood ammonia level to a ULN for blood ammonia, wherein a fasting blood ammonia level that is greater than half the ULN indicates that the subject is more likely to need a dosage adjustment of the nitrogen scavenging drug, and wherein a fasting blood ammonia level less than or equal to half the ULN indicates that the subject is less likely to need a dosage adjustment.

[0041] A nitrogen retention disorder as used herein refers to any condition associated with elevated blood nitrogen/ammonia levels. In certain embodiments, a nitrogen retention disorder may be a UCD. In other embodiments, a nitrogen retention disorder may be HE.

[0042] A nitrogen scavenging drug as used herein refers to any drug that decreases blood nitrogen and/or ammonia levels. In certain embodiments, a nitrogen scavenging drug may remove nitrogen in the form of PAGN, and in certain of these embodiments the nitrogen scavenging drug may be an orally administrable drug that contains or is metabolized to PAA. For example, a nitrogen scavenging drug may be a PAA prodrug such as PBA or HPN-100, a pharmaceutically acceptable salt of PBA such as NaPBA, or a pharmaceutically acceptable ester, acid, or derivative of a PAA prodrug. In other embodiments, a nitrogen scavenging drug may remove nitrogen via hippuric acid. In certain of these embodiments, a nitrogen scavenging drug may be benzoic acid, a pharmaceutically acceptable salt of benzoic acid such as sodium benzoate, or a pharmaceutically acceptable ester, acid, or derivative of benzoic acid.

[0043] Increasing the dosage of a nitrogen scavenging drug may refer to increasing the amount of drug per administration (e.g., an increase from a 3 mL dosage to a 6 mL dosage), increasing the number of administrations of the drug (e.g., an increase from once-a-day dosing to twice- or three-times-a-day), or any combination thereof.

[0044] A subject that has previously been administered a nitrogen scavenging drug may have been administered the drug for any duration of time sufficient to reach steady state. For example, the subject may have been administered the drug over a period of 2 to 7 days, 1 week to 2 weeks, 2 weeks to 4 weeks, 4 weeks to 8 weeks, 8 weeks to 16 weeks, or longer than 16 weeks.

[0045] In certain embodiments of the methods disclosed herein, the fasting period for obtaining a fasting blood ammonia level is overnight. In certain embodiments, the fasting period is 4 hours or more, 5 hours or more, 6 hours or more, 7 hours or more, 8 hours or more, 9 hours or more, 10 hours or more, 11 hours or more, or 12 hours or more, and in certain embodiments the fasting

period is 4-8 hours, 6-8 hours, or 8-12 hours. During the fasting period, the subject preferably does not ingest any food. In certain embodiments, the subject may also refrain from ingesting certain non-food substances during the fasting period. For example, in certain embodiments the subject does not ingest any supplements and/or nitrogen scavenging drugs during the fasting period. In certain of these embodiments, the subject may nonetheless ingest one or more drugs other than nitrogen scavenging drugs during the fasting period. In certain embodiments, the subject does not ingest any high calorie liquids during the fasting period. In certain of these embodiments, the subject does not ingest any liquids other than water during the fasting period. In other embodiments, the subject may ingest small amounts of low calorie beverages, such as tea, coffee, or diluted juices.

[0046] In certain embodiments of the methods disclosed herein, blood samples used for measuring fasting blood ammonia levels and/or ULN blood ammonias are venous blood samples. In certain embodiments, a blood sample is a plasma blood sample. Any methods known in the art may be used to obtain a plasma blood sample. For example, blood from a subject may be drawn into a tube containing heparin or ethylenediaminetetraacetic acid (EDTA). In certain embodiments, the sample can be placed on ice and centrifuged to obtain plasma within 15 minutes of collection, stored at 2-8°C (36-46°F) and analyzed within 3 hours of collection. In other embodiments, the blood plasma sample is snap frozen, stored at ≤-18°C (≤0°F) and analyzed at a later time. For example, the sample may be analyzed at 0-12 hours, 12-24 hours, 24-48, 48-96 hours after freezing, or within any other timeframe over which the sample has demonstrated stability. In certain embodiments, blood samples are taken in a laboratory or hospital setting. In certain embodiments, a single fasting blood sample is used to measure fasting blood ammonia level. However, in other embodiments, multiple fasting blood samples may be obtained. In certain embodiments, a subject's blood ammonia level may be monitored throughout the day. Further, in certain embodiments, the methods disclosed herein comprise an additional step of obtaining one or more blood samples from a subject prior to or after measuring fasting blood ammonia level.

[0047] In certain embodiments, a blood sample is analyzed immediately after collection. In other embodiments, the blood sample is stored for some period between collection and analysis. In these embodiments, the sample may be stored for less than 1 hour, 1 hour to 6 hours, 1 hour to 12 hours, 1 hour to 24 hours, or 1 hour to 48 hours. In certain of these embodiments, the blood

sample is stored at a temperature between 0-15°C, such as 2-8°C. In other embodiments, the blood sample is stored below 0°C or below -18°C.

[0048] Measurement of ammonia levels in a fasting blood sample is carried out using techniques known in the art. For example, ammonia levels may be measured using a colorimetric reaction or an enzymatic reaction. In certain embodiments, a colorimetric reaction may involve the use of bromophenol blue as an ammonia indicator. In these embodiments, ammonia may react with bromophenol blue to yield a blue dye. In certain embodiments, an enzymatic reaction may involve glutamate dehydrogenase catalyzing the reductive amination of 2-oxoglutarate with NH^{4+} and NADPH to form glutamate and $NADP^{+}$. The formation of $NADP^{+}$ formed is directly proportional to the amount of ammonia present in the blood sample. Therefore, the concentration of ammonia is measured based on a decrease in absorbance.

[0049] In certain embodiments of the methods disclosed herein, a subject exhibiting a fasting blood ammonia level less than or equal to half the ULN for blood ammonia has an average likelihood within a confidence interval that their average daily ammonia level will remain within a normal average daily ammonia level. In certain embodiments, the average likelihood of having a normal daily ammonia value is 80% to 90%. In certain embodiments, one may predict with 95% confidence that a blood ammonia level will fall within a certain range. In certain embodiments, one can predict with 95% confidence that a true probability of predicting normal values based on fasting blood ammonia is between 65% and 93%. In other embodiments, one can predict with 80% confidence that a true probability of predicting normal values based on fasting blood ammonia is at least 70%. In certain embodiments, the average likelihood of predicting normal ammonia value based on fasting blood ammonia is about 84% with 95% confidence that the true probability is between 65% and 93%.

[0050] In certain embodiments of the methods disclosed herein, a subject exhibiting a fasting blood ammonia level less than or equal to half the ULN for blood ammonia has an average likelihood within a confidence interval that their maximum daily blood ammonia level will not exceed 1.5 times the ULN for blood ammonia. In certain of these embodiments, the average likelihood is about 70% to 80%. In certain embodiments, the confidence interval is a 95% confidence interval. In certain embodiments, the average likelihood is about 75% with 95% confidence that the true probability is between 58% and 86%.

[0051] In certain embodiments of the methods disclosed herein, a subject exhibiting a fasting blood ammonia level less than or equal to half the ULN for blood ammonia has an average likelihood within a confidence interval that their maximum daily blood ammonia level will be less than 100 μmol/L. In certain of these embodiments, the average likelihood is 90% to 98%. In certain embodiments, the confidence interval is 95%. In certain embodiments, the average likelihood is about 93% with 95% confidence that the true probability is between 77% and 100%.

[0052] The maximal ammonia value refers to the maximum amount of ammonia that may be detected in a subject following consumption of meals, if repeated measurement of blood ammonia can be instituted to detect such maximum value over an extended period of time. Based on well-controlled clinical trials with repeated blood sampling over 24 hours, the maximum blood ammonia has been observed to occur following the third major meal of the day in the early to mid evening hours (4-8PM, assuming that breakfast is approximately 8AM; see, e.g., Lee 2010; Lichter-Konecki 2011).

[0053] The ULN for blood ammonia typically represents the highest level in the range of normal values, which may be influenced by a variety of factors such as the assay method, types of regents, standard reference samples used, and specifications and calibration of equipment used to perform the measurement. In certain embodiments of the methods disclosed herein, the ULN for blood ammonia is determined for a subject individually. In other embodiments, the ULN for blood ammonia may be based on measurements obtained across a range of subjects (i.e., subjects with UCD or with a particular subtype of UCD, subjects with HE, healthy subjects, etc.). In certain embodiments, the ULN for blood ammonia may represent a standard reference value disclosed in the art, such as a mean ULN developed across a particular subset of subjects. In other embodiments, the ULN for blood ammonia may represent a standard measurement that has been developed by a particular entity that performs blood draws and/or blood evaluations, such as a particular clinical laboratory. In certain embodiments, the ULN is a standard reference value utilized by the same entity that measures the fasting blood ammonia level. In these embodiments, one skilled in the art will appreciate that interpretation of average daily ammonia in subject with a nitrogen retention disorder must be made relative to the reference range of normal values at the laboratory in which the ammonia was measured. Furthermore, the units of ammonia measurement may also vary from lab to lab (e.g., μg/mL or μmoI/L), emphasizing the

importance of interpreting the subject's ammonia levels relative to the ULN at the laboratory in which the measurement was performed. In certain embodiments, the ULN for blood ammonia may be in the range of 26-64 μmol/L. In certain of these embodiments, the ULN for blood ammonia may be in the range of 32-38 μmol/L or 34-36 μmol/L, and in certain of these embodiments the ULN for blood ammonia is 35 μmol/L. In certain embodiments, the ULN for blood ammonia may be in the range of 50-65 μg/mL. In certain of these embodiments, the ULN for blood ammonia may be in the range of 55-63 μg/mL or 57-61 μg/mL, and in certain of these embodiments the ULN for blood ammonia is 59 μg/mL.

[0054] In certain embodiments, the average daily ammonia is the average amount of ammonia an individual may experience during the day, if serial blood sampling were performed for ammonia measurements. In well-controlled clinical studies, it has been established that ammonia fluctuates several fold during the day, depending on the timing of blood draw relative to food and drug intake. Due to these fluctuations, the timing of individual or serial blood sampling should be controlled relative to the timing of food and drug intake. Even serial sampling may not be enough to capture the peaks and troughs of the fluctuating ammonia values, unless samples are taken frequently enough. Therefore, obtaining a simple average of several measurements may provide inadequate or misleading information regarding the total ammonia burden a subject may experience during the day.

[0055] Provided herein are methods to better estimate a subject's average daily ammonia assessed as the area under the curve for 24-hr ammonia (ammonia $AUC_{0\text{-}24hr}$) obtained from adequate and well-spaced samples over 24 hours. This ammonia $AUC_{0\text{-}24hr}$ can be further normalized for the entire actual period of sampling, i.e., ammonia $AUC_{0\text{-}24hr}$ is divided by the sampling period (e.g., 24 hours). For example, if an AUC of 1440 μmol*hr/L is calculated using the trapezoidal rule based on 8-11 ammonia values obtained over 24 hours, then the average daily ammonia value or time-normalized $AUC_{0\text{-}24hr}$ would be equal to 1440 μmol*hr/ml divided by the sampling time of 24 hr, or 60 μmol/L. If the normal reference range at the laboratory which performed the ammonia analysis was 10-35 μmol/L, then the average daily ammonia value for this subject would be approximately 1.71 times the ULN of 35 μmol/L. Similarly, if the ammonia $AUC_{0\text{-}24hr}$ was determined to be equal to 840 μmol*hr/L based on multiple, well-spaced samples over 24 hours and analyzed at the same laboratory, and the sampling period was 24 hours, then the time-normalized $AUC_{0\text{-}24hr}$ would be 35 μmol/L. This corresponds to an

average ammonia or daily ammonia burden within the ULN. Finally, subjects with nitrogen retention disorders such as UCDs may experience a hyperammonemic crisis, which is often defined clinically as a blood level exceeding 100 μmol/L and clinical manifestations of hyperammonemia, which may require intervention to prevent irreversible hard and enable recovery.

[0056] Provided herein are methods of adjusting nitrogen scavenging drug dosage by measuring fasting blood ammonia to minimize the likelihood a subject may experience an ammonia value (Cmax) over 24 hours that exceeds 100 μmol/L. It has been found that 100 μmol/L corresponds to approximately 2-3 times the ULN in most laboratories. Previously, if a subject with a nitrogen retention disorder such as UCD had a blood ammonia level within or slightly above the normal reference range for the laboratory which performed the analysis, the subject was considered to be in good clinical control regardless of the timing of the blood draw in relation to meals and last administration of drug dose. However, it has been shown that a subject with a UCD who has a fasting blood ammonia level between the ULN and 1.5 times the ULN (e.g., 35 to 52 μmol/L) has an average likelihood of only 45% (with a 95% confidence interval of 21% to 70%) that his or her average daily ammonia is within the normal range; an average likelihood of only 35% (with a 95% confidence interval of 13% to 60%) that his or her maximal level of ammonia during the day is less than 1.5 times the ULN (e.g., 52 μmol/L); and an average likelihood of 25% that his or her maximal daily ammonia level exceeds 100 μmol/L during the day. Thus, after measuring a UCD subject's fasting blood ammonia, the dosage of a nitrogen scavenging drug may be progressively increased and/or his or her protein intake progressively decreased until the fasting ammonia value is less than or equal to half of the ULN for the local laboratory in which the ammonia analysis was performed.

[0057] In certain embodiments of the methods disclosed herein, one or more factors other than ammonia level may be taken into consideration when evaluating nitrogen scavenging drug dosage. For example, blood ammonia measurements may be combined with urinary PAGN measurements in determining whether to administer a nitrogen scavenging drug, adjusting the dosage of a nitrogen scavenging drug, or treating a nitrogen retention disorder. US Patent Publication No. 2010/0008859 discloses that urinary PAGN levels correlate more closely to PBA prodrug dosage than plasma PAA, PBA, or PAGN levels, and further discloses that PBA prodrugs are converted to urinary PAGN with a mean efficiency of 60-75%. Therefore, certain

embodiments of the methods disclosed herein comprise an additional step wherein urinary PAGN levels are measured. In certain of these embodiments, calculation of an effective dosage of nitrogen scavenging drug is based in part on a mean 60-75% conversion of PAA prodrug to urinary PAGN. For example, in certain embodiments the methods disclosed herein for determining whether to administer a nitrogen scavenging drug to a subject comprise an additional step of measuring urinary PAGN and calculating an effective initial dosage based on a mean conversion of PAA prodrug to urinary PAGN of 60-75%. Similarly, in certain embodiments the methods disclosed herein for adjusting the dosage of a nitrogen scavenging drug comprise an additional step of measuring urinary PAGN and calculating an effective dosage based on a mean conversion of PAA prodrug to urinary PAGN of 60-75%. In certain of these embodiments, the effective dosage is calculated based on a target nitrogen output. In certain embodiments, urinary PAGN may be determined as a ratio of the concentration of urinary PAGN to urinary creatinine. In certain embodiments, urinary PAGN is a factor that is taken into consideration when determining whether to administer or increase the dosage of a nitrogen scavenging drug, i.e., urinary PAGN is evaluated in combination with ammonia level to determine whether to administer or increase the dosage of the drug. In other embodiments, ammonia level alone is used to determine whether to administer or increase the dosage of a nitrogen scavenging drug, and urinary PAGN is simply used to calculate the initial or adjusted dosage.

[0058] One skilled in the art will recognize that a variety of other factors may be taken into consideration when determining the effective dosage of a nitrogen scavenging drug. For example, factors such as diet (e.g., protein intake) and endogenous waste nitrogen capacity (e.g., urea synthesis capacity) may be considered.

[0059] Provided herein in certain embodiments are kits for carrying out the methods disclosed herein. In certain embodiments, kits are provided for determining whether to administer or adjust the dosage of a nitrogen scavenging drug for a subject with a nitrogen retention disorder. The kits disclosed herein may include one or more nitrogen scavenging drugs and/or one or more reagents (e.g., bromophenol blue) or enzymes (e.g., glutamate dehydrogenase) to measure blood ammonia levels in a sample. The kit may additionally include other pigments, binders, surfactants, buffers, stabilizers, and/or chemicals necessary to obtain a blood sample and to

measure the ammonia level in the sample. In certain embodiments, the kits provided herein comprise instructions in a tangible medium.

[0060] One of ordinary skill in the art will recognize that the various embodiments described herein can be combined.

[0061] The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention. It will be understood that many variations can be made in the procedures herein described while still remaining within the bounds of the present invention. It is the intention of the inventors that such variations are included within the scope of the invention.

Examples

Example 1: Analysis of predictability of pharmacodynamic ammonia values from fasting ammonia in UCD patients:

[0062] This example demonstrates the relationship between fasting ammonia and the pharmacodynamic (PD) profile of daily ammonia in patients receiving PAA prodrugs for UCDs. Ammonia values vary many-fold over the course of 24 hours in UCD patients. As depicted in Figures 3a and 3b, venous ammonia was measured for 24 hours following one week of dosing with either NaPBA or glycerol phenylbutyrate (GPB). The graphs display ammonia values as mean ±SD over 24 hours, where time zero corresponds to just prior to dosing and breakfast (i.e., fasting state). In view of this variability in daily ammonia levels, a single measurement may not be very informative in determining whether a UCD patient is optimally dosed. The ability to predict the highest potential ammonia a UCD patient may experience during the day and the average 24-hour ammonia from a single measurement such as fasting levels has important practical implications for nitrogen scavenging drug dosing guidelines and patient management.

[0063] Data from two Phase 2 studies and one Phase 3 study comparing ammonia control assessed by 24-hour sampling during steady state treatment with HPN-100 versus NaPBA in 65 UCD patients were used for the analysis. The two Phase 2 studies include protocols UP 1204-003 and HPN-100-005 (Lee 2010; Lichter-Konecki 2011). The Phase 3 study includes protocols from HPN-100-006 (Diaz 2011).

[0064] Ammonia values obtained from different hospital laboratories with different normal ranges were normalized to a standard laboratory range of 9-35 μmol/L. The patient population included a broad range of ages, UCD subtypes, and doses of drug, and is summarized in Table 1 below.

Table 1: UCD demographics in studies UP 1204-003, HPN-100-005, and HPN-100-006:

Gender n (%)	Male	18 (27.7)
	Female	47 (72.3)
Age at screening (years)	N	65
	Mean (SD)	29.46 (15.764)
	Median	24.00
	Range	6.0-75.0
UCD diagnosis n (%)	OTC deficiency	57 (87.7)
	CPS1 deficiency	1 (1.5)
	ASS deficiency	5 (7.7)
	ASL deficiency	1 (1.5)
	Missing	1 (1.5)
Duration of NaPBA treatment (months)	N	63
	Mean (SD)	114.14 (90.147)
	Median	101.00
	Range	0.2-300.0
Daily dose NaPBA	N	64
	Mean (SD)	14.10 (6.255)
	Median	13.50
	Range	1.5-36.0

[0065] Exploratory analysis:

[0066] Several PD parameters for steady-state ammonia were explored: $AUC_{0\text{-}24hr}$, time-normalized AUC, log AUC, maximal ammonia value over 24 hours (Cmax), and average ammonia. Data from 65 subjects from all three studies with steady-state ammonia and fasting ammonia were used. Missing data were imputed per procedures specified in the protocol and statistical analysis plan, except that no imputations were made for subjects who had no PK sampling conducted while on a given study drug.

[0067] Sample collection times of 0-hr (before first daily dose) and 24-hours post-dose (before first daily dose of the following day) were both evaluated as representative of fasting ammonia. No noticeable difference in the shape or quality of the relationship due to the choice of time point was observed.

[0068] The relationship between fasting ammonia and pharmacokinetic profile was evaluated separately for HPN-100 and NaPBA, with no apparent difference in the strength or magnitude of

the relationship. Therefore, all data from both HPN-100 and NaPBA treatments were used and conclusions regarding fasting ammonia pertain to both HPN-100 and NaPBA.

[0069] The relationships between (1) fasting ammonia and $AUC_{0\text{-}24hr}$ and (2) fasting ammonia and maximum observed ammonia (Cmax) were visually explored for the whole population. The effects of the following covariates were also observed: age, weight, gender, and dietary protein intake. A positive and strong relationship was observed between fasting ammonia and $AUC_{0\text{-}24hr}$, with increasing fasting ammonia being associated with higher $AUC_{0\text{-}24hr}$ and maximum observed ammonia (Figure 2).

[0070] Prediction of $AUC_{0\text{-}24hr}$ through GEE Modeling:

[0071] The aim of this modeling was to predict average daily or highest achieved ammonia based on the subject's fasting ammonia. In order to take into account the differences in normal ranges at different laboratories, all ammonia values were normalized to a reference range of 9-35 μmol/L, and the predictions were referenced to the ULN rather than a fixed value.

[0072] Generalized Estimating Equations (GEE) were used to model the predictive ability of fasting ammonia against various ammonia PD properties. GEE methodology can be used to analyze repeated measures of categorical data, in which the repeated measures are assumed to be correlated (Liang 1986). The model allows for the specification of the assumed correlation structure without the knowledge of the magnitude of the correlation.

[0073] The 24-hour ammonia profile was divided into ordered categories using a variety of endpoints and cutpoints as follows:

1) AUC [0-1.0*ULN, >1.0*ULN];

2) AUC [0-1.5*ULN, >1.5*ULN];

3) Cmax [0-1.0*ULN, >1.0*ULN];

4) Cmax [0-1.5*ULN, >1.5*ULN]; and

5) Cmax [0-100] μmol/L.

[0074] Three levels of fasting ammonia were considered in separate models as input:

1) [0-0.5*ULN];

2) [>0.5*ULN-<1.0 ULN]; and

3) [>1.0*ULN-1.5*ULN].

[0075] Using Statistical Analysis Software (SAS) Proc Genmod, generalized linear models were fit with a logit link function. Pre-dose fasting ammonia was the only predictor variable in

the model. The repeated nature of the data (two study periods per subject) was modeled using GEE with exchangeable correlation matrix. ULN for fasting ammonia was set at 35 μmol/L. ULN for AUC over 24 hours was taken as 840 (35 μmol/L * 24 hours); i.e., the AUC which corresponds to an average daily ammonia less than or equal to 35 μmol/L, which was the normalized ULN among the participating study sites and is derived by dividing the 24-hour area under the curve by the sampling time of 24 hours. The GEE model was bootstrap-resampled 1,000 times according to the method outlined in Davison, A.C. & Hinkley, D.V., Bootstrap Methods and their Application, Cambridge University Press, London (1997), pp.358-362. The results of these models are shown in Table 2 below.

Table 2: Summary of results from GEE model to predict ability of fasting ammonia against various ammonia PD properties:

Model #	**Fasting ammonia level**	**Ammonia PK outcome**	**Probability of outcome in category**	**Bootstrap 95% c.i.**	**Bootstrap 80% c.i.**	**Bootstrap pred. error rate* (%)**
1	[0-0.5 ULN]	AUC in 24 hours [0-1.0 ULN]	0.84	0.67, 0.93	0.71, 0.89	11.5
2		AUC in 24 hours [0-1.5 ULN]	Did not converge			
3		Cmax observed [0-1.0 ULN]	0.53	0.38, 0.65	0.42, 0.61	45.8
4		Cmax observed [0-1.5 ULN]	0.76	0.61, 0.86	0.66, 0.82	23.3
5		Cmax observed [0-100]	0.93	0.78, 1.00	0.85, 0.97	5.7
6	[0-<1.0 ULN]	AUC in 24 hours [0-1.0 ULN]	0.58	0.42, 0.73	0.48, 0.68	42.8
7		AUC in 24 hours [0-1.5 ULN]	0.88	0.78, 0.97	0.82, 0.94	11.1
8		AUC in 24 hours [0-2 ULN]	0.97	0.90, 1.00	0.93, 1.00	2.2
9		Cmax observed [0-	0.21	0.11, 0.38	0.14, 0.33	20.0

		1.0 ULN]				
10		Cmax observed [0-1.5 ULN]	0.52	0.35, 0.66	0.42, 0.61	46.0
11		Cmax observed [0-2.0 ULN]	0.74	0.62, 0.85	0.91, 1.00	27.2
12		Cmax observed [0-100]	0.95	0.88, 1.00	0.66, 0.81	4.3
13	[>1.0-1.5 ULN]	AUC in 24 hours [0-1.0 ULN]	0.45	0.24, 0.71	0.30, 0.63	43
14		AUC in 24 hours [0-1.5 ULN]	Did not converge			
15		AUC in 24 hours [0-2 ULN]	0.80	0.49, 0.99	0.63, 0.92	27
16		Cmax observed [0-1.0 ULN]	Did not converge			
17		Cmax observed [0-1.5 ULN]	0.35	0.16, 0.58	0.23, 0.51	33
18		Cmax observed [0-2.0 ULN]	Did not converge			
19		Cmax observed [0-100]	Did not converge			

[0076] From Table 2 above, we can conclude that in the population of UCD patients described in Table 1, we can be 95% confident that, given a fasting ammonia less than or equal to half the ULN, the true probability of having an AUC in the range [0-840] is on average 84%, at least 67%, and as high as 93%.

[0077] Row 1 of Table 2 above suggests that a UCD patient with a fasting ammonia of 17 μmol/L as determined by a laboratory with a normal reference range of 9-35 μmol/L (i.e., a fasting ammonia in the range [0-0.5 ULN]) has an 84% chance (with a 95% confidence interval of 67% to 93%) of having a time normalized $AUC_{0\text{-}24hr}$ in the normal range [$AUC_{0\text{-}24hr}$ of 0-840 or an average daily ammonia of 35 μmol/L], a 76% chance (with a 95% confidence interval of 61% to 86%) of having a Cmax of less than l.5 ULN, and a 93% chance (with a 95% confidence

interval of 78% to 100%) of never having an ammonia of more than 100 μmol/L. Therefore, this patient would be optimally controlled and unlikely to suffer from high ammonia during the day.

[0078] This Example shows that fasting ammonia correlates strongly with daily ammonia exposure, assessed as a daily average or as maximal daily concentration, and that a target fasting value which does not exceed half of the upper level of normal for the local lab appears to be a clinically useful as well as practical predictor of ammonia values over 24 hours as well. Furthermore, this Example shows that a subject with a fasting ammonia in the range 0-0.5 ULN has an 84% chance of having an $AUC_{0\text{-}24hr}$ in the normal range (0-840 or an average daily ammonia of 35 μmol/L).

Example 2: Selecting and adjusting HPN-100 dosage based on fasting blood ammonia levels in a patient with UCD:

[0079] Patient A is an adult with UCD being managed with amino acid supplements and dietary protein restriction only. Patient A consumes neither his supplements nor food for approximately 8 hours prior to a fasting morning blood draw. A venous blood draw is performed, and fasting blood ammonia level is determined to be 52 μmol/L. This fasting blood ammonia level is compared to the ULN for blood ammonia in the laboratory performing the blood draw, which is 35 μmol/L. Based on the correlation of fasting ammonia level to average ammonia level, it is determined that Patient A's fasting blood ammonia level of approximately 1.5 times the ULN represents only a 45% chance on average of having an average ammonia during the day within the normal range. Thus, the ratio of fasting blood ammonia level to ULN for blood ammonia indicates that Patient A will benefit from treatment with a nitrogen scavenging drug.

[0080] The physician elects to treat Patient A with HPN-100. Initial dosage is determined based on body surface area or as otherwise instructed according to HPN-100 drug labeling. Patient A's body surface area is 1.4 m^2, and therefore the initial dosage is determined to be 9 mL per day or 3 mL TID, which is approximately 60% of the maximum allowed dosage per HPN-100 label. Patient A is treated with 9mL/day of HPN-l00 for at least 7 days, and returns for an additional blood draw. The fasting blood ammonia level at this time is 33 μmol/L, which is slightly below the ULN and falls into the range of 0.5 to 1.0 times normal. Patient A's blood ammonia level is monitored throughout the day after administration of a 3 mL dose of HPN-l00 with each meal. It is observed that Patient A's maximum ammonia reaches 95 μmol/L after

dinner with an average daily ammonia of 66 μmol/L, which is almost two times the upper normal range. Therefore, Patient A's dosage of HPN-100 is increased by approximately one-third to 12 mL total or 4 mL TID. Patient A returns after at least 7 days of treatment with HPN-100. Patient A's fasting ammonia level is 15 μmol/L, which is less than half of the ULN range. It is determined that Patient A has reached satisfactory ammonia control.

[0081] It is expected that if Patient A adheres to his prescribed diet, his maximal daily ammonia is not expected to exceed approximately 52 μmol/L, i.e., approximately 1.5 times the ULN, with an average likelihood of 75% with 95% confidence. The average ammonia level during the day is expected to remain within normal range with greater than 84% likelihood and 95% confidence. Moreover, Patient A's maximal daily ammonia is highly unlikely to reach 100 μmol/L during the day.

Example 3: Adjusting HPN-100 dosage based on fasting blood ammonia levels in a patient with UCD:

[0082] Patient B is an 11-year UCD patient receiving 24 pills of BUPHENYL® per day, amino acid supplements, and restricted dietary protein intake. Patient B does not consume BUPHENYL®, supplements, or food for approximately 6 hours prior to a fasting morning blood draw. A venous blood draw is performed, and fasting blood ammonia level is determined to be 40 μmol/L. This fasting blood ammonia level is compared to the ULN for blood ammonia for the laboratory performing the blood draw, which is 35 μmol/L. Based on the correlation of fasting ammonia level to average ammonia level, it is determined that Patient B's fasting blood ammonia level falling between 1 and 1.5 times the ULN represents a 55% chance of having an average ammonia during the day that is greater than the normal range, and as high as a 65% chance that her ammonia will go above 52 μmol/L or 1.5 times ULN during the day.

[0083] Based on discussion with the patient and her mother, the physician suspects that Patient B is noncompliant with her medication, and decides to change her to HPN-100. The initial dosage is determined based on the amount of BUPHENYL® Patient B was receiving, and it is determined that Patient B needs to take 10.5 mL of HPN-l00 per day. Patient B is treated with 3.5mL of HPN-100 3 times a day for at least 7 days, and returns for additional blood draws. Her fasting blood ammonia level at this time is 17 μmol/L, which is below the ULN and falls into the range of 0 to 0.5 times normal. It is determined that Patient B has reached satisfactory ammonia control.

[0084] It is expected that if Patient B adheres to her prescribed diet, her maximal daily ammonia will not go above approximately 50 μmol/L, which is less than 1.5 times the ULN. Her average ammonia level during the day is expected with greater than 84% average likelihood to remain within normal range. Moreover, there is only a small chance (7%) that Patient B's maximal daily ammonia will exceed 100 μmol/L during the day.

Example 4: Selecting and adjusting sodium benzoate dosage based on fasting blood ammonia levels in a patient with UCD:

[0085] Patient C is an adult UCD patient who is allergic to PBA and is therefore being managed with amino acid supplements and dietary protein restriction only. Patient C complains of chronic headache and frequent nausea. Patient C consumes neither his supplements nor food for approximately 8 hours prior to a fasting morning blood draw. A venous blood draw is performed, and fasting blood ammonia level is determined to be 77 μmol/L. This fasting blood ammonia level is compared to the ULN for blood ammonia for the laboratory performing the blood draw, which is 35 μmol/L. Based on the correlation of fasting ammonia level to average ammonia level, it is determined that Patient C's fasting blood ammonia level of approximately 2 times the ULN represents a high likelihood of ammonia levels going over 100 μmol/L during the day. Thus, the ratio of fasting blood ammonia level to ULN for blood ammonia indicates that Patient C will benefit from treatment with a nitrogen scavenging drug.

[0086] The physician decides to treat Patient C with 15 g of sodium benzoate per day since the patient is allergic to PBA. Patient C is treated with 15 g/day of sodium benzoate for at least 7 days, and returns for additional blood draws. Fasting blood ammonia level at this time is 35 μmol/L, which is equal to the ULN. Patient C's dosage of sodium benzoate is increased by approximately 30% to 18 grams per day. After at least 7 days of treatment, Patient C's fasting ammonia level is 15 μmol/L, which is less than half of the ULN. It is determined that Patient C has reached satisfactory ammonia control.

[0087] It is expected that if Patient C adheres to his prescribed diet and medication, his maximal daily ammonia will not exceed approximately 52 μmol/L, which is approximately 1.5 times the ULN. His average ammonia level during the day is expected with greater than 80% likelihood to remain within normal range. Moreover, Patient C's maximal daily ammonia is highly unlikely to reach 100 μmol/L during the day.

Example 5: Evaluation of the effect of ammonia control on neurocognitive outcome:

[0088] It has been shown that UCD patients are likely to suffer from diminished intelligence and impaired neurocognitive functions (Kirvitsky 2009). These neuropsychological impairments have been attributed to repeated episodes of acute hyperammonemia interspersed on chronically elevated ammonia. Abnormalities in neuropsychological function and/or brain imaging have been detected even in UCD patients with mild disorders who exhibit normal IQ and/or appear clinical normal (Gropman 2008a; Gropman 2008b). Therefore, it was hypothesized that maintaining average daily ammonia within normal limits and thereby reducing the long term ammonia burden could result in improved cognition.

[0089] The relationship between reducing ammonia burden by maintaining fasting ammonia at or close to half ULN and neuropsychological outcomes in pediatric UCD patients was explored in clinical trials. Eleven pediatric patients ages 6-17 were enrolled in short term switch over comparison of NaPBA and HPN-100 in controlling ammonia. These patients underwent 24-hr serial sample collection in a confined setting where the last sample at 24 hr was considered fasting and under supervision of the study personnel. At the end of treatment with HPN-100 the average fasting ammonia at 24-hr time point was 15.5 µmol/L or less than half ULN, indicating good clinical control. These 11 patients along with another 15 pediatric patients were enrolled in two long term studies and received HPN-100 for 12 months, during which monthly fasting ammonia were collected. At the time of enrollment and at the end of the study, all patients underwent assessment for neuropsychological outcomes including the following: BRIEF (Behavior Rating Inventory of Executive Function) to assess day-to-day executive functioning, CBCL (Child Behavior Checklist) to evaluate internalizing (e.g., mood/anxiety) and externalizing behaviors, and WASI (Wechsler Abbreviated Scale of Intelligence) to estimate of intellectual ability.

[0090] During the 12 month treatment with HPN-100, pediatric UCD patients experienced fewer episodes of acute hyperammonemia than in the 12 months preceding enrollment (5 episodes during the study versus 9 before enrollment), with peak ammonia dropping from a mean of 233 µmol/L before enrollment to 166 µmol/L during the study. Fasting ammonia remained controlled and monthly averages were at or close to half ULN, ranging from 17 to 22 µmol/L. Although patients had been instructed to remain fasting before monthly study visits, some ammonia samples were taken in a non-fasted state, resulting in average monthly ammonia of slightly above half ULN.

[0091] In pediatric patients, WASI and CBCL scores were stable in comparison to baseline. The majority of the BRIEF subscales at baseline were at or close to 65, consistent with borderline and/or clinically significant dysfunction. Among 22 pediatric subjects who completed the neuropsychological testing at 12 months, all BRIEF domains were improved (lower T scores) with means (SD) at end of study compared to baseline for Behavioral Regulation Index 53.7 (9.79) vs. 60.4 (14.03) ($p<0.05$); Metacognition Index 57.5 (9.84) vs. 67.5 (13.72) ($p<0.001$), and Global Executive Scale 56.5 (9.71) vs. 66.2 (14.02) ($p<0.001$).

[0092] The significant improvement in executive functions in this group of pediatric UCD patients indicates the importance of long term ammonia control and achieving target levels of fasting ammonia.

Example 6: Correlation of elevated PAA levels to neurological AEs in UCD and healthy subjects:

[0093] Elevated plasma levels of PAA may cause symptoms that mimic those associated with hyperammonemia, including headache, nausea, somnolence, etc. Since such symptoms are common and nonspecific, an ammonia level below half the upper limit of normal in a subject with a nitrogen retention disorder who exhibits such symptoms and is receiving a PAA prodrug would prompt a physician to check plasma PAA levels.

[0094] The relationship between elevated PAA levels and neurological AEs was evaluated in three populations: (1) 130 healthy adults dosed with 4 to 12 mL TID of GPB in a thorough QTc study, (2) 54 adult and 11 pediatric UCD patients (ages 6-17) enrolled in one of 3 protocols involving short term (2-4 week) switchover comparisons of NaPBA vs. GPB, and (3) 77 patients enrolled in two nearly identical 12-month GPB treatment protocols. In populations 1 and 2, maximal PAA (i.e., Cmax) levels were analyzed in relation to neurological AEs as defined by MEDDRA using an Exact non-parametric Mann-Whitney test and Generalized Estimating Equations (GEE) with a logit link function and effects for dose and PAA level. The relationship between PAA levels and the occurrence of the AEs reported by Thiebault was also explored in population 3.

[0095] No statistically significant relationship was observed between neurological AEs and PAA levels for either GPB or NaPBA. The odds ratio of a neurological AE occurring for each 20 μg/mL increase in PAA levels for the two drugs combined was 0.95, very close to 1. Thus, among UCD patients dosed with HPN-100 or NaPBA over the ranges used in these studies,

increasing levels of PAA (ranging up to 244 μg/mL) were not associated with an increase in neurological AEs. Similarly, in population 3, PAA levels did not increase over time and exhibited no apparent relationship to neurological AEs, which also did not increase in frequency over time. The pediatric patient with the highest PAA level (410 μg/mL) did not report neurological AEs close to the timing of the blood draw.

[0096] Unlike UCD subjects, healthy adult volunteers who reported a nervous system AE had statistically significantly higher PAA C_{max} levels than those who did not. While this analysis in healthy adults is compromised by the fact that PAA levels were not always available at the time of occurrence of the AEs, as well as by the small sample size in the higher dose groups, the odds ratio of 1.75 (p=0.006) suggests that increasing levels of PAA are associated with increased probability of experiencing a nervous system AE among healthy adults. AEs reported by healthy adults generally began within 36 hours of dosing and, among those adults who remained on study, most resolved with continued dosing.

[0097] A significant relationship between PAA levels and occurrence of neurological AEs, which generally resolved with continued dosing, was detected in healthy volunteers. Unlike in healthy adults, PAA C_{max} did not correlate with nervous system AEs in UCD patients over a similar range of doses and PAA levels. These findings may reflect metabolic differences among the populations (e.g., UCD patients exhibit high glutamine levels compared with healthy humans) and/or metabolic adaptation with continued dosing.

[0098] Population PK model building was performed on 65 UCD patients who participated in the short-term switchover Hyperion studies using NONMEM (version 7.2) based on 2981 ([PBA], [PAA], [PAGN], and urine PAGN [UPAGN])) data points from 53 adult and 11 pediatric UCD patients (ages 6-17) who participated in 3 switchover studies of NaPBA and GPB. The median GPB dose, expressed as grams of PBA per m2, was 8.85 and 7.01 for pediatric and adult subjects, respectively. Diagnostic plots and statistical comparisons were used to select among candidate models, and covariates were assessed by graphical analyses and covariate modeling. Using the final popPK model and parameter estimates, Monte Carlo simulations were performed in ~1000 virtual patients for a range of NaPBA and GPB doses to predict systemic metabolite exposure and UPAGN output.

[0099] The final model that best fit the data was characterized by (a) partial conversion of PBA to PAGN prior to reaching the systemic circulation, (b) saturable conversion of PAA to PAGN

(Km ~161ug/ml), and (c) ~60% slower PBA absorption when delivered as GPB vs. NaPBA. Body surface area (BSA) was a significant covariate such that metabolite clearance was proportionally related to BSA. Fractional presystemic metabolism of PBA was higher for adults than for pediatric patients receiving GPB (43% vs. 14%), whereas the reverse was true for NaPBA (23% vs. 43%). Predicted median PAA exposure based on simulated GPB dosing at the PBA equivalent of 13g/m2 of NaPBA was ~13%-22% lower in adults than NaPBA (Cmax = 82 vs. 106 µg/mL; $AUC_{0\text{-}24}$ = 649 vs. 829 µg.h/m) and ~13% higher in pediatric subjects ages 6-17 than NaPBA (Cmax = 154 vs. 138 µg/mL; $AUC_{0\text{-}24}$ = 1286 vs. 1154 µg.h/ml); predicted upper 95th percentile PAA exposure was below 500 µg/mL and 25%-40% lower for adult subjects on GPB versus NaPBA and similar for pediatric subjects. Simulated dosing at the PBA equivalent of ~5g/m^2 of NaPBA yielded similar and less variable PAA exposure for both drugs and for pediatric and adult patients. Recovery of PBA as UPAGN was very similar whether delivered orally as GPB or NaPBA.

[00100] These findings based on PopPK modeling and dosing simulations suggest that while most patients treated with PAA prodrugs including NaPBA or HPN-100 will have PAA levels below those reportedly associated with toxicity and while no relationship between PAA levels and neurological AEs was found on a population basis, individual patients exhibiting symptoms such as headache or nausea might be suffering from either hyperammonemia or high PAA levels and that a fasting ammonia level equal to or below half the upper limit of normal would prompt the physician to check plasma PAA levels.

[00101] As stated above, the foregoing is merely intended to illustrate various embodiments of the present invention. The specific modifications discussed above are not to be construed as limitations on the scope of the invention. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of the invention, and it is understood that such equivalent embodiments are to be included herein. All references cited herein are incorporated by reference as if fully set forth herein.

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What is claimed is:

1. A method for adjusting the dosage of glyceryl tri-[4-phenylbutyrate] in a subject being treated for a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate], the method comprising:

(a) measuring a fasting plasma ammonia level for the subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate], wherein the adjusted dosage is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

2. A method of treating a subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate], the method comprising:

(a) measuring a fasting plasma ammonia level for the subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

3. A method of administering glyceryl tri-[4-phenylbutyrate] to a subject having a urea cycle disorder, the method comprising:

(a) measuring a first fasting plasma ammonia level for the subject;

(b) comparing the first fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an initial dosage of glyceryl tri-[4-phenylbutyrate] to the subject if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

4. The method of claim 1 or 2, wherein administering the adjusted dosage of glyceryl tri-[4-phenylbutyrate] produces a normal average daily ammonia level in the subject.

5. The method of claim 1 or 2, further comprising repeating steps (a) to (c) until the subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level.

6. The method of claim 3, further comprising:

(d) measuring a second fasting plasma ammonia level for the subject;

(e) comparing the second fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(f) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the second fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

7. The method of any of claims 1-3, wherein the upper limit of normal for plasma ammonia level is 35 μmol/L.

8. The method of any of claims 1-3, wherein the upper limit of normal is specific to the laboratory in which the fasting plasma ammonia level is measured.

9. The method of any of claims 1-3, further comprising the step of determining an upper limit of normal for plasma ammonia level for the subject prior to step (b).

10. The method of claim 1 or 2, wherein the adjusted dosage is calculated by:

(i) measuring urinary phenylacetyl glutamine (PAGN) output; and

(ii) calculating an effective adjusted dosage of glyceryl tri-[4-phenylbutyrate] based on the urinary PAGN output, wherein the effective adjusted dosage is calculated based on a mean conversion of glyceryl tri-[4-phenylbutyrate] to urinary PAGN of 60 to 75%.

11. The method of claim 3, wherein the initial dosage is calculated by:

(i) determining a target urinary phenylacetyl glutamine (PAGN) output; and

(ii) calculating an effective initial dosage of glyceryl tri-[4-phenylbutyrate] based on a mean conversion of glyceryl tri-[4-phenylbutyrate] to urinary PAGN of 60 to 75%.

ABSTRACT

The present disclosure provides methods for evaluating daily ammonia exposure based on a single fasting ammonia blood level measurement, as well as methods that utilize this technique to adjust the dosage of a nitrogen scavenging drug, determine whether to administer a nitrogen scavenging drug, and treat nitrogen retention disorders.

Figure 1

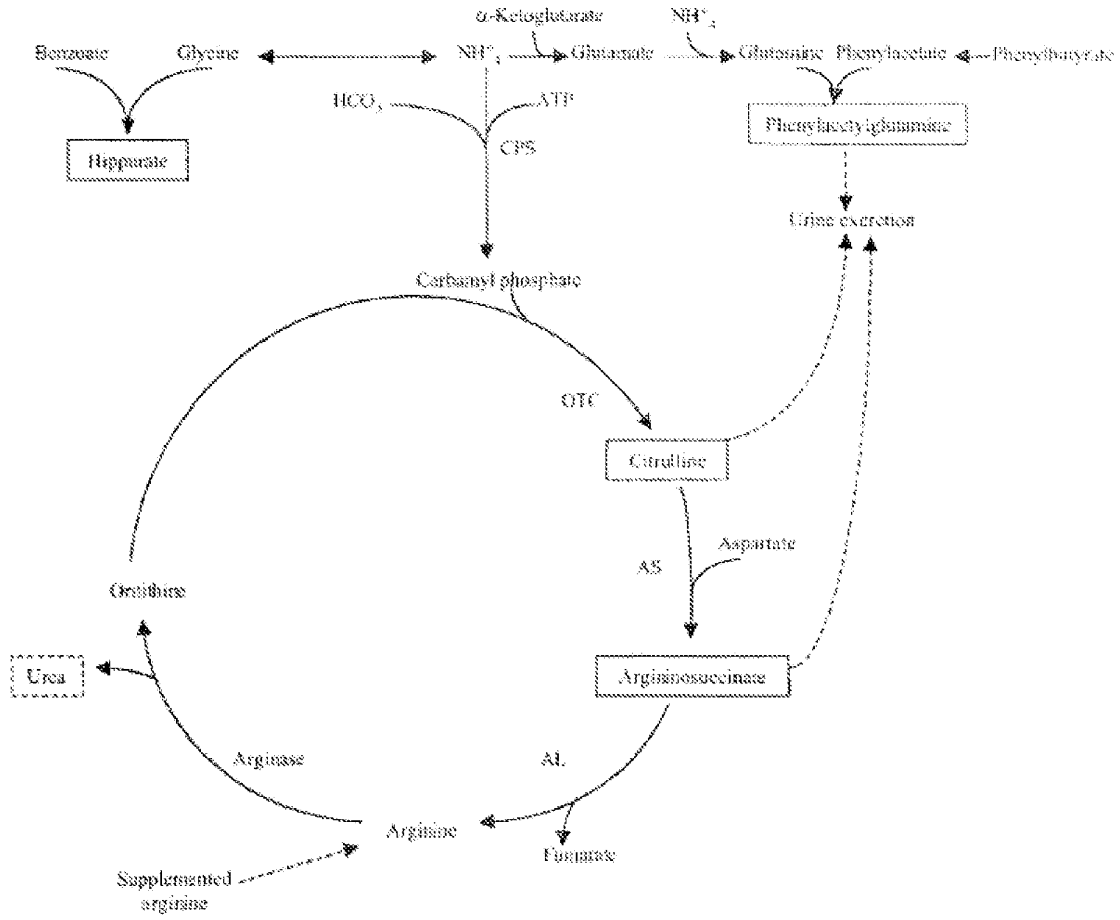

α-Ketoglutarate
NH^+_3
Benzoate
Glycine
NH^+_3
Glutamate
Glutamine
Phenylacetate
Phenylbutyrate
HCO_3
ATP
CPS
Hippurate
Phenylacetylglutamine
Urine excretion
Carbamyl phosphate
OTC
Citrulline
Aspartate
AS
Ornithine
Urea
Argininosuccinate
Arginase
AL
Arginine
Fumarate
Supplemented arginine

Figure 2

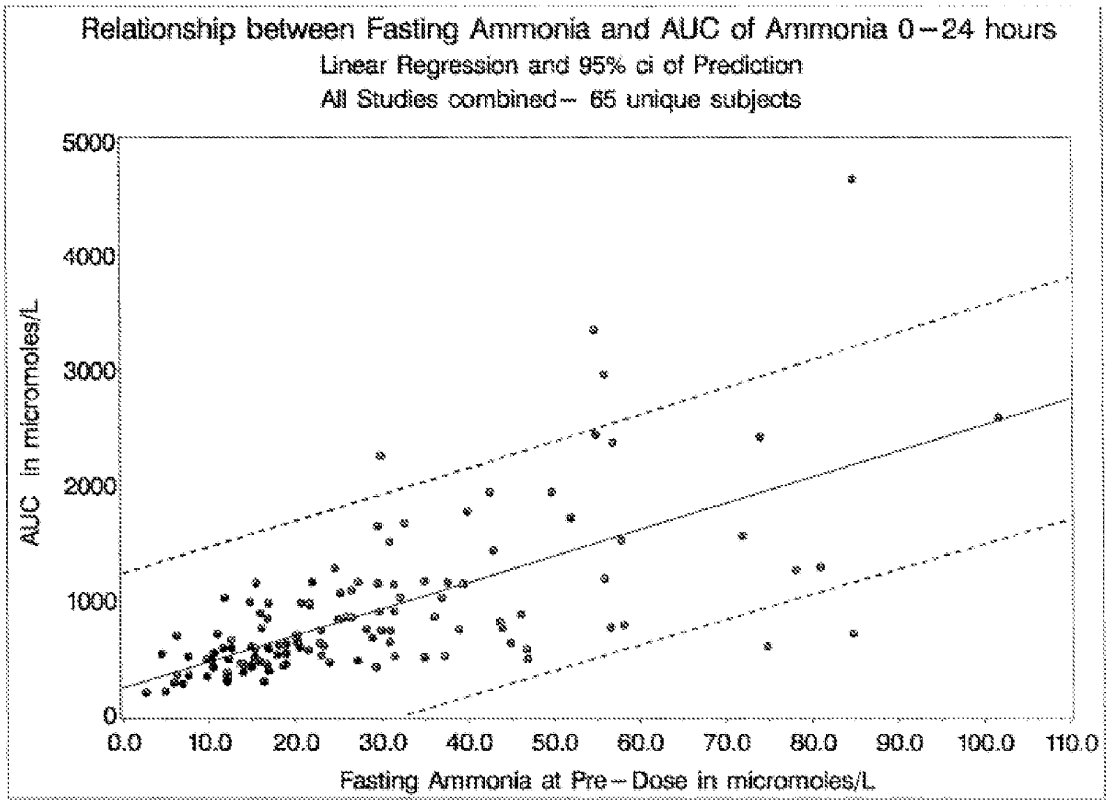
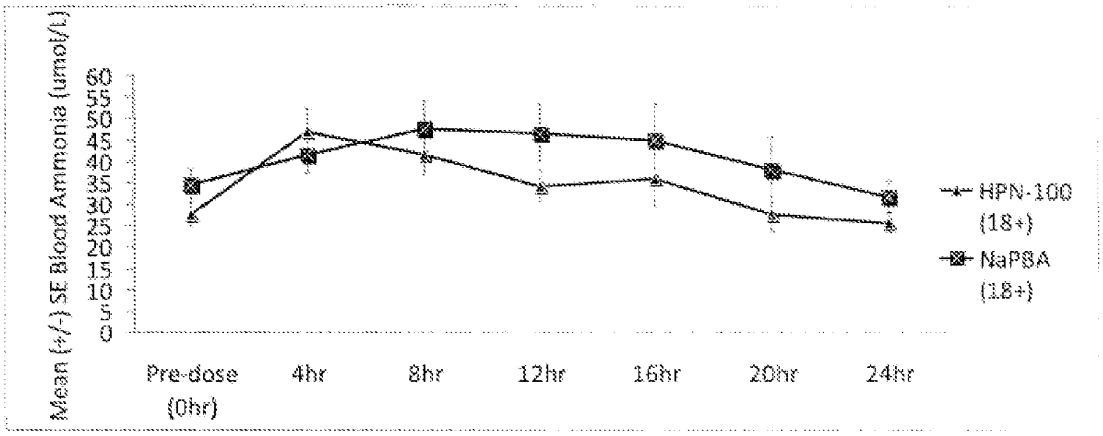
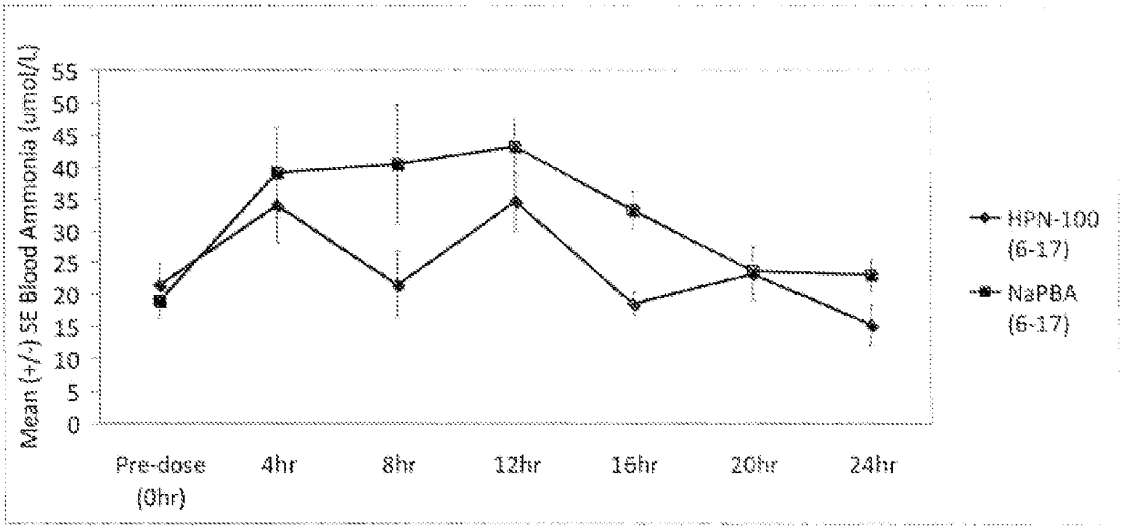

Relationship between Fasting Ammonia and AUC of Ammonia 0 – 24 hours
Linear Regression and 95% ci of Prediction
All Studies combined – 65 unique subjects
AUC in micromoles/L
5000
4000
3000
2000
1000
0
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
Fasting Ammonia at Pre – Dose in micromoles/L

Figure 3

A.


Mean (+/-) SE Blood Ammonia (umol/L)
60
55
50
45
40
35
30
25
20
15
10
5
0
Pre-dose (0hr)
4hr
8hr
12hr
16hr
20hr
24hr
HPN-100 (18+)
NaPBA (18+)

B.


Mean (+/-) SE Blood Ammonia (umol/L)
55
50
45
40
35
30
25
20
15
10
5
0
Pre-dose (0hr)
4hr
8hr
12hr
16hr
20hr
24hr
HPN-100 (6-17)
NaPBA (6-17)

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Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	HOR0026-201TC2-US

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
	P1	4,284,647	08-18-1981	The Johns Hopkins University	
	P2	4,457,942	07-03-1984	Brusilow, S.W.	
	P3	5,654,333	08-05-1997	The United States Of America As Represented By The Department Of Health And Human Services	
	P4	5,968,979	10-19-1999	Brusilow Enterprises Llc	
	P5	6,060,510	05-09-2000	Brusilow Enterprises Llc	
	P6	6,083,984	07-04-2000	Brusilow Enterprises Llc	
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	P8	8,094,521	01-10-2012	Nightengale Products LLC	
	P9	8,404,215	03-26-2013	Hyperion Therapeutics, Inc.	
	P10	8,642,012	02-04-2014	Hyperion Therapeutics, Inc.	
	P11	9,078,865	7-14-2015	Lee	
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	P13	2004/0229948	11-18-2004	Marshall L. Summar et al	
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	P19	2012/0022157	01-26-2012	Ucyclyd Pharma, Inc	
	P20	2012/0220661	08-30-2012	Baylor College of Medicine	
	P21	2013/0210914	08-15-2013	Hyperion Therapeutics, Inc.	
	P22	2013/0281530	10-24-2013	Scharschmidt, et al	
	P23	2014/0142186	05-22-2014	Hyperion Therapeutics, Inc.	
	P24	2015/0105469	4-16-2015	Scharschmidt et al.	
	P25	2015/0094278	3-26-15	Scharschmidt et al.	

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	F1	WO1994/22494	10-13-1994	The DuPont Merck Pharmaceutical Company		
	F2	WO2005/053607	06-16-2005	Medicis Pharmaceutical Corporation		
	F3	WO2006/056794	06-01-2006	UCL Business PLC		
	F4	WO2007/005633	01-11-2007	Navinta LLC		
	F5	WO2009/087474	07-16-2009	Akthelia Pharmaceuticals		
	F6	WO2009/134460	11-05-2009	Ucyclyd Pharma, Inc.		
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	F8	WO2012/028620	03-08-2012	Inserm		
	F9	WO2013/048558	04-04-2013	Hyperion Therapeutics, Inc.		
	F10	WO2013/158145	10-24-2013	Hyperion Therapeutics, Inc.		

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	D1	AHRENS, M. et al. (January 2001). "Consensus Statement From a Conference for the Management of Patients With Urea Cycle Disorders." Supp. Journal of Pediatrics 138(1):S1-S5.	
	D2	AMBROSE, A.M. et al., "Further Studies on the Detoxification of Phenylacetic Acid", 101 J. Bio. Chem. 669 (1933).	
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	D5	ANDA Notice Letter, Lupin Ltd. to Horizon Therapeutics, Inc.. Re: Notification of Invalidity, Unenforceability, and/or Noninfringement for U.S. Patent Nos. 8,404,215 and 8,642,012 Pursuant to § 505(j)(2)(B)(ii) and (iv) of the Federal Food, Drug, and Cosmetic Act, Sept. 4, 2015	
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	D28	BRUSILOW, S.W. et al., "Urea Cycle Enzymes", in THE METABOLIC AND MOLECULAR BASES OF INHERITED DISEASES 1187 (C.R. Scriver et al. eds. 1995).	
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	D30	BURLINA, A.B. et al., "Long-Term Treatment with Sodium Phenylbutyrate in Ornithine Transcarbamylase-Deficient Patients", 72 Molecular Genetics and Metabolism 351-355 (2001).	
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	D36	Center for Drug Evaluation and Research, Clinical Pharmacology and Biopharmaceutics Review for New Drug Application No. 20-645 (Ammonul®) (2005).	
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	D41	CHUNG, Y.L., et al., (2000) "A Novel Approach for Nasopharyngeal Carcinoma Treatment Uese Phenylbutyrate as a Protein Kinase C Modulator: Implications for Radiosensitization and EBV-Targeted Therapy," Clin Cancer Res 6:1452-1458.	
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	D44	COLLINS, A.F. et al., "Oral Sodium Phenylbutyrate Therapy in Homozygous Beta Thalassemia: A Clinical Trial", 85 Blood 43 (1995).	
	D45	Combined Search and Examination Report mailed on Oct. 9, 2009, for Great Britain Patent Application No. GB0915545.8, filed on Aug. 27, 2009, eight pages.	
	D46	Combined Search and Examination Report mailed on Sep. 9, 2010, for Great Britain Patent Application No. 1013468.2, filed on Aug. 27, 2009, six pages.	
	D47	'Complaint for Patent Infringement', Hyperion Therapeutics, Inc. v. Par Pharmaceuticals, Inc. Filed in U.S. District Court for the Eastern District of Texas, April 23, 2014.	
	D48	'Complaint for Patent Infringement', Horizon Therapeutics, Inc. v. Lupin Ltd. and Lupin Pharmaceuticals Inc. Filed in U.S. District Court for the District of New Jersey, October 19, 2015.	
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	D63	European Medicines Agency, Annex I: Summary of Product Characteristics for Ammonaps.	

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				Art Unit	TBD
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	D105	International Search Report and Written Opinion for PCT/US09/30362, mailed Mar. 2, 2009, 8 pages.	
	D106	International Search Report and Written Opinion for PCT/US2009/055256, mailed Dec. 30, 2009, 13 pages.	
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Sheet | 16 | of | 21

Complete if Known	
Application Number	TBD
Filing Date	TBD
First Named Inventor	Bruce Scharschmidt
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	HOR0026-201TC2-US

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[6]
	D159	MUNOZ, S. J., "Hepatic Encephalopathy," Med. Clin. N. Am. 92:795-812 (2008).	
	D160	NASSOGNE, M.C., "Urea Cycle Defects: Management and Outcome", 28 J. Inherit. Metab. Dis. 407 (2005).	
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	D162	New England Consortium of Metabolic Programs, Acute Illness Protocol: Urea Cycle Disorders: The Infant/Child with Citrullinemia, adapted from Summar, M and Tuchman, M, Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders, 138 J. Peds. Suppl. S6 (2001).	
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				Art Unit	TBD
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	D171	PRAPHANPROJ, V. et al., "Three Cases of Intravenous Sodium Benzoate and Sodium Phenylacetate Toxicity Occurring in the Treatment of Acute Hyperammonemia," 23 J. Inherited Metabolic Disease 129 (2000).	
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	D174	ROCKEY, D. C., et al., "Randomized, Controlled, Double Blind Study of Glycerol Phenylbutyrate in Patients with Cirrhosis and Episodic Hepatic Encephalopathy," Hepatology 56:248(A) (2012).	
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	D181	Search and Examination Report for British Patent Application No. GB 0915545.8, dated Oct. 8, 2009, 5 pages.	
	D182	SEIKI et al., "Homogenous Pharmaceutical Emulsions Containing Nonsteriodal Analogesics and Inflammation Inhibitors"Chemical Abstract, Vol. 116, No. 46308.	

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	D192	SUMMAR, M. et al., "Unmasked Adult-Onset Urea Cycle Disorders in the Critical Care Setting", 21 Crit. Care Clin. S1 (2005).	
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	D194	SUMMAR, M.L. et al., "Diagnosis, Symptoms, Frequency and Mortality of 260 Patients with Urea Cycle Disorders From a 21-Year, Multicentre Study of Acute Hyperammonemic Episodes", 97 Acta Paediatr. 1420 (Oct. 2008, e-pub. Jul. 17, 2008).	

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Sheet | 19 | of | 21

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	D207	United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2013/71333 mailed March 28, 2014.	
	D208	United States Patent and Trademark Office, International Search Report and Written Opinion dated January 16, 2015 for PCT/US14/58489.	
	D209	United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/ US2014/060543 dated January 23, 2015.	
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				Art Unit	TBD
(use as many sheets as necessary)				**Examiner Name**	TBD
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	D219	XIE, G., et al., (2012) "Role of Differentiation of Liver Sinusoidal Endothelial Cells in Progression and Regression of Hepatic Fibrosis in Rats," Gastroenterology 142:S918	
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Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorized/Internet Communications Authorization Withdrawn

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS		
	Application No.	Not yet assigned
	Filing Date	Herewith
	First Named Inventor	Bruce Scharschmidt
	Art Unit	Not yet assigned
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☑ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

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I am the

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/Lauren L. STEVENS/ — Signature

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Atty Docket No.: HOR0026-201TC2-US

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Scharschmidt et al.	)
			) Group Art Unit:
Serial No.	:	To be assigned	) To be assigned
			)
Filed	:	Herewith	)
			) Examiner:
			) To be assigned

Title: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

NOTICE OF RELATED LITIGATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant hereby notifies the U.S. Patent and Trademark Office that the subject matter of the present application is involved in litigation in the United States.

Specifically, Par Pharmaceutical, Inc. ("Par") sent a PIV notice letter to Hyperion Therapeutics, Inc. ("Hyperion") on March 12, 2014 providing notice that Par had filed an Abbreviated New Drug Application ("ANDA") with respect to RAVICTI® (Glycerol Phenylbutyrate) Oral Liquid, with a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") alleging that U.S. Patent Nos. 8,404,215 and 8,642,012 are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the Watson drug product.

Under 21 U.S.C. § 355(j)(5)(B)(iii), Hyperion had forty-five days from receipt of the ANDA notice letter to file suit against Watson for patent infringement. Accordingly, on April 23, 2014, Hyperion brought suit on those patents against Par in the United States District Court for the Eastern District of Texas, Marshall Division. The Complaint alleged that Par infringes U.S. Patent Nos. 8,404,215 and 8,642,012. Subsequently, in May of 2015, Horizon Pharma plc ("Horizon") acquired Hyperion Therapeutics, Inc. through a merger. The subject application is a

continuation of U.S. Patent No. 8,404,215. The Complaint is provided with an SB-08 filed concurrently herewith.

Lupin Ltd. ("Lupin") sent a PIV notice letter to Horizon Therapeutics, Inc. ("Horizon") on Sept. 4, 2015 providing notice that Lupin had filed an Abbreviated New Drug Application ("ANDA") with respect to RAVICTI® (Glycerol Phenylbutyrate) Oral Liquid, with a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") alleging that U.S. Patent Nos. 8,404,215 and 8,642,012 are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the Lupin drug product.

Under 21 U.S.C. § 355(j)(5)(B)(iii), Horizon had forty-five days from receipt of the ANDA notice letter to file suit against Lupin for patent infringement. Accordingly, on October 19, 2015, Horizon brought suit on those patents against Lupin Ltd. And Lupin Pharmaceuticals, Inc. in the United States District Court for the District of New Jersey. The Complaint alleged that Lupin infringes U.S. Patent Nos. 8,404,215 and 8,642,012. The subject application is a continuation of U.S. Patent No. 8,404,215. The Complaint is provided with an SB-08 filed concurrently herewith.

Respectfully submitted,

By /Lauren L. STEVENS/

Lauren L. Stevens
Attorney for Applicant
Registration No. 36,691
(650) 387-3813

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/958,259	Filing Date 12/03/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT

12/03/2015	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					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 number found in the appropriate box in column 1.

LIE
/LASHAWN MARKS/

This collection of information is required by 37 CFR 1.16. 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, 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 and select option 2.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/958,259

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			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	10 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 420 =	420
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).						0.00
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			TOTAL	2020

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	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/958,259	12/03/2015	Bruce Scharschmidt	HOR0026-201TC2-US

CONFIRMATION NO. 3046

101325
GLOBAL PATENT GROUP - HOR
1005 NORTH WARSON ROAD
SUITE 404
SAINT LOUIS, MO 63132

OC000000079332314

Date Mailed: 12/15/2015

NOTICE OF ACCEPTANCE OF AUTHORIZATION TO PERMIT ACCESS TO APPLICATION VIA PRIORITY DOCUMENT EXCHANGE

This is in response to the applicant's authorization to permit access to the application-as-filed by participating offices under 37 CFR 1.14(h)(1) submitted on 12/03/2015.

The authorization to permit access to the application under 37 CFR 1.14(h)(1) is accepted.

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**.

/rmohamed/

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/958,259	12/03/2015	1629	2020	HOR0026-201TC2-US	10	4

CONFIRMATION NO. 3046

101325
GLOBAL PATENT GROUP - HOR
1005 NORTH WARSON ROAD
SUITE 404
SAINT LOUIS, MO 63132

FILING RECEIPT

OC000000079332310

Date Mailed: 12/15/2015

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)

Bruce Scharschmidt, San Francisco, CA;
Masoud Mokhtarani, Walnut Creek, CA;

Applicant(s)

Horizon Therapeutics, Inc., Deerfield, IL;

Power of Attorney: The patent practitioners associated with Customer Number 101325

Domestic Priority data as claimed by applicant

This application is a CON of 14/816,674 08/03/2015
which is a CON of 13/775,000 02/22/2013 PAT 9095559
which is a CON of 13/417,137 03/09/2012 PAT 8404215
which claims benefit of 61/542,100 09/30/2011
and claims benefit of 61/564,668 11/29/2011

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: Yes

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: 12/11/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/958,259**

Projected Publication Date: 03/24/2016

Non-Publication Request: No

Early Publication Request: No

Title

METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

Preliminary Class

514

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Bruce Scharschmidt et al.
Title:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
Appl. No.:	14/958,259
Filing Date:	December 3, 2015
Examiner:	To be assigned
Art Unit:	To be assigned
Confirmation Number:	3046

PRELIMINARY AMENDMENT UNDER 37 CFR 1.115

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Prior to examination, please amend the application as indicated on the following pages.

This paper contains:

Amendments to the Claims are reflected on page 2 of this document.

Remarks/Arguments follow the Amendments to the Claims.

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1.-21. (Cancelled)

22. (New) A method of treating a subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level,

wherein the upper limit of normal for plasma ammonia level is in the range of 26-64 μmol/L.

23. (New) The method of claim 22, wherein the upper limit of normal for plasma ammonia level is in the range of 32-38 μmol/L.

24. (New) The method of claim 23, wherein the upper limit of normal for plasma ammonia level is in the range of 34-36 μmol/L.

25. (New) The method of claim 22, wherein the upper limit of normal for plasma ammonia level is in the range of 55-63 µg/mL.

26. (New) The method of claim 25, wherein the upper limit of normal for plasma ammonia level is in the range of 57- 61 µg/mL.

27. (New) The method of claim 26, wherein the upper limit of normal for plasma ammonia level is 59 µg/mL.

28. (New) The method of claim 22, further comprising repeating steps (a) to (c) until the subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level.

29. (New) The method of claim 22, wherein the adjusted dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

30. (New) A method of treating a subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level,

wherein the upper limit of normal for plasma ammonia level is in the range of 50-65 µg/L.

31. (New) The method of claim 30, wherein the upper limit of normal for plasma ammonia level is in the range of 55-63 µg/mL.

32. (New) The method of claim 31, wherein the upper limit of normal for plasma ammonia level is in the range of 57-61 µg/mL.

33. (New) The method of claim 32, wherein the upper limit of normal for plasma ammonia level is 59 µg/mL.

34. (New) The method of claim 30, further comprising repeating steps (a) to (c) until the subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level.

35. (New) The method of claim 30, wherein the adjusted dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

36. (New) A method of treating a pediatric subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the pediatric subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

37. (New) The method of claim 36, further comprising repeating steps (a) to (c) until the pediatric subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level.

38. (New) The method of claim 36, wherein the adjusted dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

39. (New) A method of treating an adult subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the adult subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

40. (New) The method of claim 39, further comprising repeating steps (a) to (c) until the adult subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level.

41. (New) The method of claim 39, wherein the adjusted dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

REMARKS

Applicant respectfully requests that the foregoing amendments be made prior to examination of the present application. Claims 12-21 have been cancelled without prejudice or disclaimer. Claims 22-41 have been added. No new matter has been introduced by those amendments.

Applicant believes that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone or email, if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

January 15, 2016
Date

/Brock D. Levin/
Brock Levin, Reg. No. 65,040
Attorney for Applicants

Global Patent Group, LLC
1005 North Warson Road Suite 201
St. Louis, Missouri 63132
TELE: (314) 812-8020
FAX: (314) 685-2300

Electronic Patent Application Fee Transmittal

Application Number:	14958259
Filing Date:	03-Dec-2015
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Brock D. Levin/Vicki Truman
Attorney Docket Number:	HOR0026-201TC2-US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Independent claims in excess of 3	1201	1	420	420
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**420**

Electronic Acknowledgement Receipt	
EFS ID:	24634825
Application Number:	14958259
International Application Number:	
Confirmation Number:	3046
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Brock D. Levin/Vicki Truman
Filer Authorized By:	Brock D. Levin
Attorney Docket Number:	HOR0026-201TC2-US
Receipt Date:	15-JAN-2016
Filing Date:	03-DEC-2015
Time Stamp:	14:14:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$420
RAM confirmation Number	502
Deposit Account	504297
Authorized User	TRUMAN, VICKI
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		20160115_Preliminary_Amendment.pdf	33194 4ed7fea68a4f68df096230740efd3ae63fdfa440	yes	6

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Preliminary Amendment	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	6

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30864 9aaeb43c6f526d09c65580dd3f91355c1819af9c	no	2

Warnings:

Information:

Total Files Size (in bytes):	64058

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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.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/958,259	Filing Date 12/03/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/15/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						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 number found in the appropriate box in column 1.

LIE
/ANDREA FREEMAN/

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/958,259	Filing Date 12/03/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/15/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						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 number found in the appropriate box in column 1.

LIE
/LASHAWN MARKS/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/958,259	12/03/2015	Bruce Scharschmidt	HOR0026-201TC2-US	3046

101325 7590 01/29/2016

GLOBAL PATENT GROUP - HOR
1005 NORTH WARSON ROAD
SUITE 404
SAINT LOUIS, MO 63132

EXAMINER
RAO, SAVITHA M

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
01/29/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

admin@globalpatentgroup.com
vtruman@globalpatentgroup.com
LStevens@horizonpharma.com

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Commissioner for Patents
United States Patent and Trademark Office
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Doc Code:
TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/958,259

1. THE REQUEST FILED 12/3/15 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination
A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Terri Johnson at 571-272-2991

/Terri Johnson/ Paralegal Specialist

[*Signature*] (Title)

Office of Petitions: Routing Sheet

Application No. 14/958,259

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [X] **GRANTED**
- [ ] **DISMISSED**
- [ ] **DENIED**

Office of Petitions: Decision Count Sheet

Mailing Month: 1

Application No.: 14958259

14958259

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456
For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: Johnson, Terri

Count (1) - Palm Credit 14/958,259

Decision: GRANT

FINANCE WORK NEEDED
☐ Select Check Box for YES

GRANT

Decision Type: 643 - Track One request

643

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED
☑ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on: *1/25/2016*

Office of Petitions Internal Document - Ver. 5.0

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/958,259	12/03/2015	Bruce Scharschmidt	HOR0026-201TC2-US	3046

101325 7590 02/05/2016

GLOBAL PATENT GROUP - HOR
1005 NORTH WARSON ROAD
SUITE 404
SAINT LOUIS, MO 63132

EXAMINER	
RAO, SAVITHA M	

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
02/05/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

admin@globalpatentgroup.com
vtruman@globalpatentgroup.com
LStevens@horizonpharma.com

Office Action Summary	Application No. 14/958,259	Applicant(s) SCHARSCHMIDT ET AL.	
	Examiner SAVITHA RAO	Art Unit 1621	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/15/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *22-41* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *22-41* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, 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.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *12/03/2015*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

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

DETAILED ACTION

Claims 22-41 are pending and are under consideration in the instant office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 12/03/2015 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits. See attached copy of the PTO-1449.

Priority

This application is a continuation of application 14/816,674 dated 08/03/2015 (granted as patent 9,254,278) which is a continuation of applicaiton 13/775,000 dated 02/22/2013 (granted as patent 9,095,559) which is a continuation of application 13/147,317 dated 03/19/2012 (granted as a patent number 8,404,215) which claims priority under 35 U.S.C 119 (e) from provisional application serial No. 61/564668 filed 11/29/2011 and provisional application no 61/542100 filed on 09/30/2011.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled

out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 22-41 are rejected on the ground of nonstatutory double patenting over claims 2, 4 and 7-10 of U.S. Patent 9, 254,278 ('278) , claims 3-6 of U. S. Patent No 8,404,215 ('215) and claims1-15 of U.S. Patent No 9,095,559 ('559) claims since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patents.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter.

Instant independent claims 22 and 30 are drawn towards a method of treating a subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level

less than the upper limit of normal for plasma ammonia level, the method comprising: (a) measuring a fasting plasma ammonia level for the subject; (b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and (c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level, wherein the upper limit of normal for plasma ammonia level is in the range of 26-64 pmol/L or in the range of 50-65 pg/L,

Instant independent claims 36 and 39 are drawn to a method of treating a pediatric subject or an adult subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising: (a) measuring a fasting plasma ammonia level for the pediatric subject; (b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and (c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

Claim 2 of ‘278 states as follows:

2. A method of treating a subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate], the method comprising:

(a) measuring a fasting plasma ammonia level for the subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

. The other limitations instantly claimed are recited in the claims of parent patent '278. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are rendered prima facia obvious to a person of ordinary skill in the art to utilize the specific agent instantly claimed which is taught in in the methods of claim 2 of '278 where in an urea cycle disorder. It is also noted that the steps in following the instant method is the same as that claimed in '278.

Claim 3 of '215 states as follows

3. A method of treating a subject with a nitrogen retention disorder who has previously been administered an initial dosage of a nitrogen scavenging drug comprising:
a) measuring a fasting blood ammonia level for the subject;
b) compering the fasting blood ammonia level to the upper limit of normal for blood ammonia level; and
c) administering an adjusted dosage of the nitrogen scavenging drug that is greater than the initial dosage if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.

Dependent claims recite the nitrogen retention disorder to be urea cycle disorder ('215 claims 4) and the nitrogen scavenging drug to be glyceryl tri-(4-phenylbutyrate) (reference claim 6) which is instantly claimed. The other limitations instantly claimed in are recited in the claims of parent patent '215. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are rendered prima facia obvious to a person of ordinary skill in the art to utilize the specific agent instantly claimed in the methods of claim 1 and 3 of '215 where in the nitrogen retention disorder is an urea cycle disorder. It is also noted that the steps in following the instant method is the same as that claimed in '215.

Claims 1-3 of '559 recites as follows:

What is claimed is:

1. A method for adjusting the dosage of glyceryl tri-[4-phenylbutyrate] in a subject being treated for a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate], wherein the adjusted dosage is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

2. A method of treating a subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

3. A method of administering glyceryl tri-[4-phenylbutyrate] to a subject having a urea cycle disorder, the method comprising:

(a) measuring a first fasting plasma ammonia level for the subject;

(b) comparing the first fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an initial dosage of glyceryl tri-[4-phenylbutyrate] to the subject if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level and less than the upper limit of normal for plasma ammonia level.

'559 recites a method for treating urea cycle in a subject by administering glyceryl-tri-(4-phenylbutyrate). The other limitations instantly claimed are recited in the claims of parent patent '559. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are rendered prima facia obvious to a person of ordinary skill in the art as they are both drawn to the same

subject matter. It is also noted that the steps in following the instant method is the same as that claimed in '559.

Claim 22-41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-12 of U.S. Patent No. 8,642,012 (co-pending '012)

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Instant claims 22-41 recite as stated above

Claims 1of '012 recite as follows:

1. A method of treating a patient having a urea cycle disorder comprising (a) determining a target urinary phenylacetyl glutamine (PAGN) output (b) calculating an effective initial dosage of a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt of PBA, wherein the effective dosage of PAA prodrug is calculated based on a mean conversion of PAA prodrug to urinary PAGN of about 60%; and (c) administering the effective initial dosage of PAA prodrug to the patient.

'012 recite a method for treating urea cycle in a subject by administering glyceryl-tri-(4-phenylbutyrate). The other limitations instantly are recited in the claims of parent patent '012. Although the conflicting claims are not identical, they are not patentably

distinct from each other. The instant claims are rendered prima facia obvious to a person of ordinary skill in the art as they are both drawn to the same subject matter. It is also noted that the steps in following the instant method is the same as that claimed in '012.

.

Conclusion

Claims 22-41 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melanie McCormick can be reached at 571-272-8037. 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.

/SAVITHA RAO/
Primary Examiner, Art Unit 1621

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NEWS	12	APR 9	CAS Expands Global Patent Coverage - The Eurasian Patent Organization Becomes 63rd Authority on CA/CAplus
NEWS	13	APR 16	DWPI Database (WPINDEX, WPIDS, WPIX) Enhanced with Numerical Property Search Feature
NEWS	14	APR 23	RSS Delivery for STN Alerts (SDIs) is Now Available on STN
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NEWS	20	MAY 30	INPADOC Databases-Enhanced Coverage of US Citation Data
NEWS	21	JUN 01	INPADOCDB: Legal Status in Original Language Available
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NEWS	23	JUL 05	More Frequent Updates to the Emtree Thesaurus in Embase on STN Provide Earlier Access to the Latest Drug and Medical Terminology
NEWS	24	JUL 18	INPADOCDB: Enhanced Display Options
NEWS	25	JUL 19	Upcoming Reload of AEROSPACE: Effect on SDIs, Manual Profiles and Saved Answers
NEWS	26	JUL 30	Launch of new PQSciTech Database, Created from 25 Individual CSA Databases Allows More Efficient Searching on STN
NEWS	27	JUL 30	Reload of ENCOMPPAT/2 Databases
NEWS	28	JUL 30	More Experimental Property Data in CAS REGISTRY
NEWS	29	AUG 1	Reload of ReaxysFile on STN - Significantly More Content Added and Updates are Resumed
NEWS	30	AUG 1	Redesigned CAS Website to be Launched on August 5, 2012

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 NEWS 31  AUG  6  INPADOC: German Patent Coverage Resumed
 NEWS 32  SEP 10  Get More Current Reaction Information with Daily Updates to
                  CASREACT
 NEWS 33  SEP 10  Predict when CAS REGISTRY Hits 70 Million
 NEWS 34  SEP 20  Reload of METADEX - Effect on SDIs and Saved Answers
 NEWS 35  SEP 24  Expanded Embase Database Coverage on STN Includes More
                  Biomedical and Pharmacological Content from Conferences
 NEWS 36  OCT 19  MARPAT Backfile Expansion Update
 NEWS 37  OCT 23  Embase's Emtree Thesaurus Updated
 NEWS 38  OCT 29  New Japanese Full-Text Patent Database Now Available on STN
 NEWS 39  NOV 13  Upcoming Reload of AGRICOLA - Effect on SDIs, Manual Profiles
                  and Saved Answers

 NEWS EXPRESS 23 MAY 2012 CURRENT WINDOWS VERSION IS V8.5.1,
              AND CURRENT DISCOVER FILE IS DATED 20 JULY 2012.

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FILE LAST UPDATED: 15 Nov 2012  (20121115/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  September 2012
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  September 2012

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reclassification data for the fourth quarter of 2012.
```

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substance identification.

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=> s "nitrogen scavenging"
        951198 "NITROGEN"
          4883 "NITROGENS"
        954619 "NITROGEN"
                 ("NITROGEN" OR "NITROGENS")
         44689 "SCAVENGING"
            20 "SCAVENGINGS"
         44704 "SCAVENGING"
                 ("SCAVENGING" OR "SCAVENGINGS")
L1          32 "NITROGEN SCAVENGING"
                 ("NITROGEN"(W)"SCAVENGING")

=> s l1 and PAA
         10799 PAA
           573 PAAS
         11191 PAA
                 (PAA OR PAAS)
L2           1 L1 AND PAA

=> d l2 ibib ab

L2   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:        2010:708850  CAPLUS
DOCUMENT NUMBER:         154:477123
TITLE:                   Phase 2 comparison of a novel ammonia scavenging agent
                         with sodium phenylbutyrate in patients with urea cycle
                         disorders: Safety, pharmacokinetics and ammonia
                         control
AUTHOR(S):               Lee, Brendan; Rhead, William; Diaz, George A.;
                         Scharschmidt, Bruce F.; Mian, Asad; Shchelochkov,
                         Oleg; Marier, J. F.; Beliveau, Martin; Mauney, Joseph;
                         Dickinson, Klara; Martinez, Antonia; Gargosky,
                         Sharron; Mokhtarani, Masoud; Berry, Susan A.
CORPORATE SOURCE:        Baylor College of Medicine, Houston, TX, R814, USA
SOURCE:                  Molecular Genetics and Metabolism (2010), 100(3),
                         221-228
                         CODEN: MGMEFF; ISSN: 1096-7192
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Glycerol phenylbutyrate (glyceryl tri (4-phenylbutyrate)) (GPB) is being
     studied as an alternative to sodium phenylbutyrate (NaPBA) for the
     treatment of urea cycle disorders (UCDs).  This phase 2 study explored the
     hypothesis that GPB offers similar safety and ammonia control as NaPBA,
     which is currently approved as adjunctive therapy in the chronic
     management of UCDs, and examined correlates of 24-h blood ammonia.  Methods:
     An open-label, fixed sequence switch-over study was conducted in adult UCD
     patients taking maintenance NaPBA.  Blood ammonia and blood and urine
     metabolites were compared after 7 days (steady state) of TID dosing on
     either drug, both dosed to deliver the same amount of phenylbutyric acid
     (PBA).  Results: Ten subjects completed the study.  Adverse events were
     comparable for the two drugs; 2 subjects experienced hyperammonemic events
     on NaPBA while none occurred on GPB.  Ammonia values on GPB were
     .apprx.30% lower than on NaPBA (time-normalized AUC = 26.2 vs. 38.4
```

μmol/L; Cmax = 56.3 vs. 79.1 μmol/L; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time-normalized AUC) by post hoc anal. Systemic exposure (AUC0-24) to PBA on GPB was 27% lower than on NaPBA (540 vs. 739 μg h/mL), whereas exposure to phenylacetic acid (PAA) (575 vs. 596 μg h/mL) and phenylacetylglutamine (PAGN) (1098 vs. 1133 μg h/mL) were similar. Urinary PAGN excretion accounted for .apprx.54% of PBA administered for both NaPBA and GPB; other metabolites accounted for <1%. Intact GPB was generally undetectable in blood and urine. Blood ammonia correlated strongly and inversely with urinary PAGN (r = -0.82; p < 0.0001) but weakly or not at all with blood metabolite levels. Conclusions: Safety and ammonia control with GPB appear at least equal to NaPBA. Urinary PAGN, which is stoichiometrically related to nitrogen scavenging, may be a useful biomarker for both dose selection and adjustment for optimal control of venous ammonia.

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     FILE 'CAPLUS' ENTERED AT 07:19:34 ON 16 NOV 2012
L1           32 S "NITROGEN SCAVENGING"
L2            1 S L1 AND PAA

     FILE 'STNGUIDE' ENTERED AT 07:20:35 ON 16 NOV 2012

=> s l1 and butyric
             0 "NITROGEN"
             0 "SCAVENGING"
             0 "NITROGEN SCAVENGING"
                 ("NITROGEN"(W)"SCAVENGING")
             0 BUTYRIC
L3           0 L1 AND BUTYRIC

=> s l1 and phenylbutyric
             0 "NITROGEN"
             0 "SCAVENGING"
             0 "NITROGEN SCAVENGING"
                 ("NITROGEN"(W)"SCAVENGING")
             0 PHENYLBUTYRIC
L4           0 L1 AND PHENYLBUTYRIC

=> s nitrogen
L5           0 NITROGEN
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=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       1.62      15.07

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FILE COVERS 1907 - 16 Nov 2012  VOL 157 ISS 22
FILE LAST UPDATED: 15 Nov 2012  (20121115/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  September 2012
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  September 2012

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s nitrogen
        951198 NITROGEN
          4883 NITROGENS
L6      954619 NITROGEN
                 (NITROGEN OR NITROGENS)

=> s l6 and scavenging
         44689 SCAVENGING
            20 SCAVENGINGS
         44704 SCAVENGING
                 (SCAVENGING OR SCAVENGINGS)
L7        1850 L6 AND SCAVENGING

=> s l7 and PAA
         10799 PAA
           573 PAAS
         11191 PAA
                 (PAA OR PAAS)
L8           1 L7 AND PAA

=> d l8 ibib ab

L8   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:        2010:708850  CAPLUS
DOCUMENT NUMBER:         154:477123
TITLE:                   Phase 2 comparison of a novel ammonia scavenging
```

agent with sodium phenylbutyrate in patients with urea cycle disorders: Safety, pharmacokinetics and ammonia control

AUTHOR(S): Lee, Brendan; Rhead, William; Diaz, George A.; Scharschmidt, Bruce F.; Mian, Asad; Shchelochkov, Oleg; Marier, J. F.; Beliveau, Martin; Mauney, Joseph; Dickinson, Klara; Martinez, Antonia; Gargosky, Sharron; Mokhtarani, Masoud; Berry, Susan A.

CORPORATE SOURCE: Baylor College of Medicine, Houston, TX, R814, USA

SOURCE: Molecular Genetics and Metabolism (2010), 100(3), 221-228
CODEN: MGMEFF; ISSN: 1096-7192

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Glycerol phenylbutyrate (glyceryl tri (4-phenylbutyrate)) (GPB) is being studied as an alternative to sodium phenylbutyrate (NaPBA) for the treatment of urea cycle disorders (UCDs). This phase 2 study explored the hypothesis that GPB offers similar safety and ammonia control as NaPBA, which is currently approved as adjunctive therapy in the chronic management of UCDs, and examined correlates of 24-h blood ammonia. Methods: An open-label, fixed sequence switch-over study was conducted in adult UCD patients taking maintenance NaPBA. Blood ammonia and blood and urine metabolites were compared after 7 days (steady state) of TID dosing on either drug, both dosed to deliver the same amount of phenylbutyric acid (PBA). Results: Ten subjects completed the study. Adverse events were comparable for the two drugs; 2 subjects experienced hyperammonemic events on NaPBA while none occurred on GPB. Ammonia values on GPB were .apprx.30% lower than on NaPBA (time-normalized AUC = 26.2 vs. 38.4 μmol/L; Cmax = 56.3 vs. 79.1 μmol/L; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time-normalized AUC) by post hoc anal. Systemic exposure (AUC0-24) to PBA on GPB was 27% lower than on NaPBA (540 vs. 739 μg h/mL), whereas exposure to phenylacetic acid (PAA) (575 vs. 596 μg h/mL) and phenylacetylglutamine (PAGN) (1098 vs. 1133 μg h/mL) were similar. Urinary PAGN excretion accounted for .apprx.54% of PBA administered for both NaPBA and GPB; other metabolites accounted for <1%. Intact GPB was generally undetectable in blood and urine. Blood ammonia correlated strongly and inversely with urinary PAGN ($r = -0.82$; $p < 0.0001$) but weakly or not at all with blood metabolite levels. Conclusions: Safety and ammonia control with GPB appear at least equal to NaPBA. Urinary PAGN, which is stoichiometrically related to nitrogen scavenging, may be a useful biomarker for both dose selection and adjustment for optimal control of venous ammonia.

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=> s PAA prodrug
         10799 PAA
           573 PAAS
         11191 PAA
                 (PAA OR PAAS)
         17954 PRODRUG
         20950 PRODRUGS
         27897 PRODRUG
                 (PRODRUG OR PRODRUGS)
L9           0 PAA PRODRUG
                 (PAA(W)PRODRUG)
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=> s PAA
         10799 PAA
           573 PAAS
L10      11191 PAA
                (PAA OR PAAS)

=> s L10 and prodrug
         17954 PRODRUG
         20950 PRODRUGS
         27897 PRODRUG
                (PRODRUG OR PRODRUGS)
L11          9 L10 AND PRODRUG

=> d l11 1-9 ibib ab

L11  ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:         2012:1197939  CAPLUS
DOCUMENT NUMBER:          157:426609
TITLE:                    Determination of phenylbutyric acid and its metabolite
                          phenylacetic acid in different tissues of mouse by
                          liquid chromatography with tandem mass spectrometry
                          and its application in drug tissue distribution
AUTHOR(S):                Marahatta, Anu; Bhandary, Bidur; Lee, Mi-Rin; Kim,
                          Do-Sung; Lee, Yong Chul; Kim, So-Ri; Kim, Hyung-Ryong;
                          Chae, Han-Jung
CORPORATE SOURCE:         Department of Pharmacology, School of Medicine,
                          Chonbuk National University, Jeonju, 560-182, S. Korea
SOURCE:                   Journal of Chromatography, B: Analytical Technologies
                          in the Biomedical and Life Sciences (2012), 903,
                          118-125
                          CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER:                Elsevier B.V.
DOCUMENT TYPE:            Journal; (online computer file)
LANGUAGE:                 English
AB   Endoplasmic reticulum (ER) stress is associated with various human diseases.
     Phenylbutyric acid (PBA) is a well-known chemical chaperone that regulates ER
     stress.  The main objective of this study was to develop a simple, rapid,
     and sensitive method for the simultaneous determination of phenylbutyric acid
and
     its metabolite, phenylacetic acid (PAA).  A LC-MS/MS anal. using neg.
     electrospray ionization was used.  Samples were analyzed by multiple
     reaction monitoring (MRM) in 15 min of total run time, using d11-PBA and
     d7-PAA as internal stds.  The limit of quantification was 1 μg/g for
     tissue and 0.8 μg/mL for plasma.  Recoveries for plasma and tissues
     were higher than 81% for both PBA and PAA.  The inter-day and intra-day
     accuracy and precision were within ±15%.  We then further successfully
     validated this method by applying it to determine the tissue distribution of
     PBA and its metabolite PAA after i.p. injection of PBA at a dose of 500
     mg/kg in mice.  The maximum concns. of PBA and PAA in plasma and tissues
     were seen at 15 min and 45 min, resp.  The PBA plasma concentration was 15-fold
     higher than the concentration in the kidney, whereas the PAA plasma
concentration was
     6-fold higher than the concentration in the liver.  The area under the curve
     decreased in the order of plasma > kidney > liver > heart > muscle > lung
     for PBA and plasma > liver > kidney > heart > muscle > lung for PAA.
     The tissue to plasma ratio ranged from 0.007 to 0.063 for PBA and 0.016 to
     0.109 for PAA.  In summary, the LC-ESI-MS method developed in this study
     is simple, sensitive and reliable.
REFERENCE COUNT:          23    THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS
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L11  ANSWER 2 OF 9  CAPLUS  COPYRIGHT 2012 ACS on STN
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ACCESSION NUMBER: 2011:1275522 CAPLUS
DOCUMENT NUMBER: 156:626560
TITLE: Macromolecular prodrugs based on synthetic polyaminoacids: drug delivery and drug targeting in antitumor therapy
AUTHOR(S): Cavallaro, Gennara; Pitarresi, Giovanna; Giammona, Gaetano
CORPORATE SOURCE: Dipartimento di Chimica e Tecnologie Farmaceutiche, Universita degli Studi di Palermo, Palermo, 90123, Italy
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) (2011), 11(18), 2382-2389
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. In the last twenty years a depth study on potential pharmaceutical applications of synthetic polymers at protein-like structure as carrier for macromol. prodrug production has been performed in academia and in industry. In particular α,β-poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA), α,β-polyaspartylhydrazide (PAHy), poly(glutamic acid) (PGA), poly(aspartic acid) (PAA) and polylysine (PLL) have been extensively studied in this field. In the present review, the use of PHEA, PAHy, PGA as starting materials to prepare macromol. prodrugs is reported and drug delivery and targeting aspects have been considered.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:122221 CAPLUS
DOCUMENT NUMBER: 154:243916
TITLE: Reducible and degradable polymer prodrug and preparation method thereof
INVENTOR(S): Huang, Jin; Yu, Jiahui; Fan, Honglei
PATENT ASSIGNEE(S): Wuhan University of Technology, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 12pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 101954091	A	20110126	CN 2010-10507432	20101014

PRIORITY APPLN. INFO.: CN 2010-10507432 20101014
AB The title polymer prodrug has a chemical structural formula of MPEG-graft-SS-PAA-T, wherein MPEG is polyethylene glycol monomethyl ether with mol. weight of 475-5000 Da, SS-PAA is disulfide bond-containing polycystamine, and T represents medicine mol., e.g. camptothecin. The title method comprises Michael addition reaction of diacryloyl cystamine to obtain disulfide bond-containing alkynyl polycystamine, linking alkynyl with azimino-containing medicine mol. via click reaction, reacting the alkynyl with azido-ended polyethyleneglycol monomethyl ether via click reaction. The method is highly effective, safe and simple.

L11 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1063363 CAPLUS
DOCUMENT NUMBER: 153:626843

TITLE: Nanomicelle with long-term circulation and enhanced stability of camptothecin based on mPEGylated α,β-poly (L-aspartic acid)-camptothecin conjugate
AUTHOR(S): Zhang, Weilu; Huang, Jin; Fan, Naiqian; Yu, Jiahui; Liu, Yongbiao; Liu, Shiyuan; Wang, Daxin; Li, Yaping
CORPORATE SOURCE: Institutes for Advanced Interdisciplinary Research, East China Normal University, Shanghai, 200062, Peop. Rep. China
SOURCE: Colloids and Surfaces, B: Biointerfaces (2010), 81(1), 297-303
CODEN: CSBBEQ; ISSN: 0927-7765
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 153:626843
AB To enhance the stability and long-term circulation of camptothecin (CPT), mPEGylated α,β-poly (L-aspartic acid)-CPT conjugates were synthesized, and used to fabricate nanomicelle. Firstly, α,β-poly (L-aspartic acid) derivative (PAA-der) containing alkyne groups was synthesized via the ring-opening of PSI with propargyl amine. Then, azide-functionalized CPT derivs. (CPT-N3) and azide-terminated poly (ethylene glycol) Me ether (mPEG-N3) were conjugated with PAA-der by click cycloaddn. to give mPEG-graft-PAA-CPT conjugates. The formation of mPEG-graft-PAA-CPT nanomicelles was confirmed by fluorescence spectrophotoscopy and particle size measurements. It was found that all the nanomicelles showed spherical shapes with size about 178 nm. MPEG-graft-PAA-CPT nanomicelles showed good storage stability, even incubation at 37° for 60 days, and improved the stability of CPT lactone form in aqueous media. A steady release rate of CPT was kept for 72 h, suggested the great potential of mPEG-graft-PAA-CPT nanomicelles as polymer prodrug of CPT.
OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2005:622439 CAPLUS
DOCUMENT NUMBER: 143:278873
TITLE: Mechanism of poly(acrylic acid) acceleration of antithrombin inhibition of thrombin: implications for design of novel heparin mimics
AUTHOR(S): Monien, Bernhard H.; Cheang, Kai I.; Desai, Umesh R.
CORPORATE SOURCE: Departments of Medicinal Chemistry and Pharmacy and Institute for Structural Biology and Drug Discovery, Virginia Commonwealth University, Richmond, VA, 23298, USA
SOURCE: Journal of Medicinal Chemistry (2005), 48(16), 5360-5368
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The bridging mechanism of antithrombin inhibition of thrombin is a dominant mechanism contributing a massive .apprx.2500-fold acceleration in the reaction rate and is also a key reason for the clin. usage of heparin. Our recent study of the antithrombin-activating properties of a carboxylic acid-based polymer, poly(acrylic acid) (PAA), demonstrated a surprisingly high acceleration in thrombin inhibition (Monien, B. H.; Desai, U. R. J. Med. Chemical 2005, 48, 1269). To better understand this interesting phenomenon, we have studied the mechanism of PAA-dependent

acceleration in antithrombin inhibition of thrombin. Competitive binding studies with low-affinity heparin and a heparin tetrasaccharide suggest that PAA binds antithrombin in both the pentasaccharide- and the extended heparin-binding sites, and these results are corroborated by mol. modeling. The salt-dependence of the KD of the PAA-antithrombin interaction shows the formation of five ionic interactions. In contrast, the contribution of nonionic forces is miniscule, resulting in an interaction that is significantly weaker than that observed for heparins. A bell-shaped profile of the observed rate constant for antithrombin inhibition of thrombin as a function of PAA concentration was observed, suggesting that inhibition proceeds through the "bridging" mechanism. The knowledge gained in this mechanistic study highlights important rules for the rational design of orally available heparin mimics.

OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2000:890604 CAPLUS

DOCUMENT NUMBER: 134:242530

TITLE: Mucoadhesive drug carriers based on complexes of poly(acrylic acid) and PEGylated drugs having hydrolyzable PEG-anhydride-drug linkages

AUTHOR(S): Lele, B. S.; Hoffman, A. S.

CORPORATE SOURCE: Bioengineering Department, University of Washington, Seattle, WA, 98195, USA

SOURCE: Journal of Controlled Release (2000), 69(2), 237-248
CODEN: JCREEC; ISSN: 0168-3659

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have designed a new mucoadhesive drug delivery formulation based on H-bonded complexes of poly(acrylic acid) (PAA) or poly(methacrylic acid) (PMAA) with the poly(ethylene glycol) (PEG), of a (PEG)-drug conjugate. The PEGylated prodrugs are synthesized with degradable PEG-anhydride-drug bonds for eventual delivery of free drug from the formulation. In this work we have used indomethacin as the model drug which is PEGylated via anhydride bonds to the PEG. The complexes are designed first to dissociate as the formulation swells in contact with mucosal surfaces at pH 7.4, releasing PEG-indomethacin, which then hydrolyzes to release free drug and free PEG. We found that as MW of PAA increases, the dissociation rate of the complex decreases, which results in decreased rate of release of the drug. On the other hand, the drug release from PEG-indomethacin alone and from solid mixture of PEG-indomethacin+PAA was much faster than that from the H-bonded complexes. Due to the differences in the thermal stability, PMAA complex exhibited slightly faster drug release than that of the PAA complex of comparable MW. These H-bonded complexes of degradable PEGylated drugs with bioadhesive polymers should be useful for mucosal drug delivery.

OS.CITING REF COUNT: 78 THERE ARE 78 CAPLUS RECORDS THAT CITE THIS RECORD (78 CITINGS)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 1997:5450 CAPLUS

TITLE: Patent evaluation anti-infectives Phosphonic acid prodrugs with improved antiviral activity

CORPORATE SOURCE: Univ. California, USA

SOURCE: Expert Opinion on Therapeutic Patents (1996), 6(12), 1331-1333

CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This patent discloses lipid derivs. as prodrugs for antiviral agents. It relates particularly to lipid prodrugs of phosphonic acids and their use in the treatment of viral infections. The invention claims a series of improved prodrugs of phosphonoformate (PFA), phosphonoacetate (PAA) and their analogs, with increased in vitro antiviral activity over the parent compds. against human cytomegalovirus (HCMV), herpes simplex virus (HSV) and human immunodeficiency virus (HIV).

L11 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 1994:631238 CAPLUS
DOCUMENT NUMBER: 121:231238
ORIGINAL REFERENCE NO.: 121:42186h,42187a
TITLE: Inhibition of Human Immunodeficiency Virus Type 1 Replication by Phosphonoformate- and Phosphonoacetate-2',3'-Dideoxy-3'-thiacytidine Conjugates
AUTHOR(S): Charvet, Anne-Sophie; Camplo, Michel; Faury, Philippe; Graciet, Jean-Christophe; Mourier, Nicolas; Chermann, Jean-Claude; Kraus, Jean-Louis
CORPORATE SOURCE: Laboratoire de Chimie Biomoleculaire, Faculte des Sciences de Luminy, Marseille, 13288, Fr.
SOURCE: Journal of Medicinal Chemistry (1994), 37(14), 2216-23
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The synthesis of potential "combined prodrugs" where phosphonoformic acid (PFA) or phosphonoacetic acid (PAA) was attached to the 5'-O- or N4-position of 2',3'-dideoxy-3'-thiacytidine (BCH-189) is described. The anti-HIV-1 activity of 11 analogs I [R1 = Ac, COCH2P(O)(OEt)2, COCH2P(O)(OH)2, COP(O)(OMe)2, COP(O)(OH)2, (CH2)4O2CP(O)(OEt)2, H; R2 = COP(O)(OMe)2, COP(O)(OH)2, COP(O)(OEt)2, COCH2P(O)(OEt)2, COCH2P(O)(OH)2, P(O)(OH)CO2Et, P(O)(OH)CO2H] was determined in MT-4 cells. Of these compds., the IC50 of I [R1 = Ac, R2 = COCH2P(O)(OEt)2, COCH2P(O)(OH)2, COP(O)(OMe)2, COP(O)(OH)2; 1 = COCH2P(O)(OH)2, R2 = H; R1 = R2 = COP(O)(OH)2] ranged from 0.2 to 100 μM, while IC50 for BCH-189 in this system was 0.1 μM. In vitro hydrolysis of the various esters or amides in human plasma indicated that these agents were relatively stable in the presence of plasma esterases with t1/2 values of up to 120 min. Moreover, lipophilicity of these compds. (partition coefficient) was determined in order to establish correlation between lipophilicity and diffusion of BCH-189 analogs into the cells. The active compds. may exert their effects by extracellular or intracellular hydrolysis to BCH-189, but intrinsic anti-HIV-1 activity of some adducts, themselves, may also be involved.
OS.CITING REF COUNT: 34 THERE ARE 34 CAPLUS RECORDS THAT CITE THIS RECORD (34 CITINGS)

L11 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 1985:67342 CAPLUS
DOCUMENT NUMBER: 102:67342
ORIGINAL REFERENCE NO.: 102:10499a,10502a
TITLE: Physicochemical and antitumor characteristics of some polyamino acid prodrugs of mitomycin C
AUTHOR(S): Roos, C. F.; Matsumoto, Satoshi; Takakura, Yoshinobu; Hashida, Mitsuru; Sezaki, Hitoshi
CORPORATE SOURCE: Fac. Pharm. Sci., Kyoto Univ., Kyoto, 606, Japan
SOURCE: International Journal of Pharmaceutics (1984), 22(1), 75-87

```
                          CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Mitomycin C (MMC) conjugates with the polyamino acids: poly-L-glutamic
     acid (PGA; mol. weight 11,000 and 60,000), poly-L-aspartic acid (PAA; mol.
     weight 14,000) and poly-L-lysine (PLY; mol. weight 13,000) were synthesized to
     obtain more information about the application of polyamino acids as high
     mol. weight carriers.  Some physicochem. and antitumor characteristics of
     these conjugates were investigated.  Gel filtration confirmed covalent
     binding and provided information about the mol. sizes.  The release rates
     of MMC  [50-07-7] from conjugates were determined in vitro.  The PAA and PGA
     (mol. weight 11,000) conjugates acted as neg. charged mols. in their
     interaction with ion exchangers.  The PLY conjugate showed a pos. charge
     and was able to bind to Ehrlich ascites carcinoma cells in vitro.  The
     effects of 1 h exposure of mouse L1210 leukemia cells to the conjugates
     were evaluated using cell culture system.  In this experiment, only the PLY
     conjugate showed better effects than MMC.  Continuous exposure to the
     conjugates showed a similar effect to MMC.  In vivo, less toxicity was
     found for the conjugates than for MMC.  The PGA (mol. weight 11,000) and PLY
     conjugates showed slightly higher effects against P388 leukemia than MMC,
     while no toxic doses were reached.
OS.CITING REF COUNT:     14    THERE ARE 14 CAPLUS RECORDS THAT CITE THIS
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     FILE 'CAPLUS' ENTERED AT 07:19:34 ON 16 NOV 2012
L1           32 S "NITROGEN SCAVENGING"
L2            1 S L1 AND PAA

     FILE 'STNGUIDE' ENTERED AT 07:20:35 ON 16 NOV 2012
L3            0 S L1 AND BUTYRIC
L4            0 S L1 AND PHENYLBUTYRIC
L5            0 S NITROGEN

     FILE 'CAPLUS' ENTERED AT 07:31:11 ON 16 NOV 2012
L6       954619 S NITROGEN
L7         1850 S L6 AND SCAVENGING
L8            1 S L7 AND PAA
L9            0 S PAA PRODRUG
L10       11191 S PAA
L11           9 S L10 AND PRODRUG

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 NEWS  3  APR  9  CAS Expands Global Patent Coverage - The Eurasian Patent
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 NEWS 13  JUN 11  Keep Current with Weekly SDI Packages Now Available on STN
 NEWS 14  JUL 05  More Frequent Updates to the Emtree Thesaurus in Embase on STN
                  Provide Earlier Access to the Latest Drug and Medical
                  Terminology
 NEWS 15  JUL 18  INPADOCDB: Enhanced Display Options
 NEWS 16  JUL 19  Upcoming Reload of AEROSPACE: Effect on SDIs, Manual
                  Profiles and Saved Answers
 NEWS 17  JUL 30  Launch of new PQSciTech Database, Created from 25 Individual
                  CSA Databases Allows More Efficient Searching on STN
 NEWS 18  JUL 30  Reload of ENCOMPPAT/2 Databases
 NEWS 19  JUL 30  More Experimental Property Data in CAS REGISTRY
 NEWS 20  AUG  1  Reload of ReaxysFile on STN - Significantly More Content Added
                  and Updates are Resumed
 NEWS 21  AUG  1  Redesigned CAS Website to be Launched on August 5, 2012
 NEWS 22  AUG  6  INPADOC: German Patent Coverage Resumed
 NEWS 23  SEP 10  Get More Current Reaction Information with Daily Updates to
                  CASREACT
 NEWS 24  SEP 10  Predict when CAS REGISTRY Hits 70 Million
 NEWS 25  SEP 20  Reload of METADEX - Effect on SDIs and Saved Answers
 NEWS 26  SEP 24  Expanded Embase Database Coverage on STN Includes More
                  Biomedical and Pharmacological Content from Conferences
 NEWS 27  OCT 19  MARPAT Backfile Expansion Update
 NEWS 28  OCT 23  Embase's Emtree Thesaurus Updated
 NEWS 29  OCT 29  New Japanese Full-Text Patent Database Now Available on STN
 NEWS 30  NOV 13  Upcoming Reload of AGRICOLA - Effect on SDIs, Manual Profiles
                  and Saved Answers
 NEWS 31  NOV 19  Reload of IMSPATENTS - Effect on SDIs, Manual profiles and
                  Saved answers
 NEWS 32  NOV 27  INPADOC: The New Cooperative Patent Classification Is Now
                  Available.
 NEWS 33  DEC  3  Enhanced CASREACT Coverage on STN - A New Source of Prior Art
 NEWS 34  DEC 10  New SDI STANDARD Option Streamlines SDI Set-ups on STN

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USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  November 2012

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=> s "nitrogen scavenger" or "nitrogen scavenging"
        957090 "NITROGEN"
          4893 "NITROGENS"
        960515 "NITROGEN"
                 ("NITROGEN" OR "NITROGENS")
         38770 "SCAVENGER"
         40998 "SCAVENGERS"
         65856 "SCAVENGER"
                 ("SCAVENGER" OR "SCAVENGERS")
             9 "NITROGEN SCAVENGER"
                 ("NITROGEN"(W)"SCAVENGER")
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          4893 "NITROGENS"
        960515 "NITROGEN"
                 ("NITROGEN" OR "NITROGENS")
         45123 "SCAVENGING"
            21 "SCAVENGINGS"
         45139 "SCAVENGING"
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            33 "NITROGEN SCAVENGING"
                ("NITROGEN"(W)"SCAVENGING")
L1          40 "NITROGEN SCAVENGER" OR "NITROGEN SCAVENGING"

=> s l1 and ammonia
        312555 AMMONIA
           201 AMMONIAS
        312639 AMMONIA
                (AMMONIA OR AMMONIAS)
L2          11 L1 AND AMMONIA

=> d l2 1-11 ibib ab

L2   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:        2012:1307676  CAPLUS
TITLE:                   Urinary phenylacetylglutamine as dosing biomarker for
                         patients with urea cycle disorders
AUTHOR(S):               Mokhtarani, M.; Diaz, G. A.; Rhead, W.;
                         Lichter-Konecki, U.; Bartley, J.; Feigenbaum, A.;
                         Longo, N.; Berquist, W.; Berry, S. A.; Gallagher, R.;
                         Bartholomew, D.; Harding, C. O.; Korson, M. S.;
                         McCandless, S. E.; Smith, W.; Vockley, J.; Bart, S.;
                         Kronn, D.; Zori, R.; Cederbaum, S.; Dorrani, N.;
                         Merritt, J. L.; Sreenath-Nagamani, Sandesh; Summar,
                         M.; LeMons, C.; Dickinson, K.; Coakley, D. F.; Moors,
                         T. L.; Lee, B.; Scharschmidt, B. F.
CORPORATE SOURCE:        601 Gateway Blvd, Hyperion Therapeutics, South San
                         Francisco, CA, 94080, USA
SOURCE:                  Molecular Genetics and Metabolism (2012), 107(3),
                         308-314
                         CODEN: MGMEFF; ISSN: 1096-7192
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal; (online computer file)
LANGUAGE:                English
AB   We have analyzed pharmacokinetic data for glycerol phenylbutyrate (also
     GT4P or HPN-100) and sodium phenylbutyrate with respect to possible dosing
     biomarkers in patients with urea cycle disorders (UCD).These analyses are
     based on over 3000 urine and plasma data points from 54 adult and 11
     pediatric UCD patients (ages 6-17) who participated in three clin. studies
     comparing ammonia control and pharmacokinetics during steady state
     treatment with glycerol phenylbutyrate or sodium phenylbutyrate.  All
     patients received phenylbutyric acid equivalent doses of glycerol
     phenylbutyrate or sodium phenylbutyrate in a cross over fashion and
     underwent 24-h blood samples and urine sampling for phenylbutyric acid,
     phenylacetic acid and phenylacetylglutamine.Patients received
     phenylbutyric acid equivalent doses of glycerol phenylbutyrate ranging from
     1.5 to 31.8 g/day and of sodium phenylbutyrate ranging from 1.3 to 31.7
     g/day.  Plasma metabolite levels varied widely, with average fluctuation
     indexes ranging from 1979% to 5690% for phenylbutyric acid, 843% to 3931%
     for phenylacetic acid, and 881% to 1434% for phenylacetylglutamine.  Mean
     percent recovery of phenylbutyric acid as urinary phenylacetylglutamine
     was 66.4 and 69.0 for pediatric patients and 68.7 and 71.4 for adult
     patients on glycerol phenylbutyrate and sodium phenylbutyrate, resp.  The
     correlation with dose was strongest for urinary phenylacetylglutamine
     excretion, either as morning spot urine (r = 0.730, p < 0.001) or as total
     24-h excretion (r = 0.791 p < 0.001), followed by plasma
     phenylacetylglutamine AUC24-hour, plasma phenylacetic acid AUC24-hour and
     phenylbutyric acid AUC24-hour.  Plasma phenylacetic acid levels in adult
     and pediatric patients did not show a consistent relationship with either
     urinary phenylacetylglutamine or ammonia control.The findings are
     collectively consistent with substantial yet variable pre-systemic (1st
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pass) conversion of phenylbutyric acid to phenylacetic acid and/or phenylacetylglutamine. The variability of blood metabolite levels during the day, their weaker correlation with dose, the need for multiple blood samples to capture trough and peak, and the inconsistency between phenylacetic acid and urinary phenylacetylglutamine as a marker of waste nitrogen scavenging limit the utility of plasma levels for therapeutic monitoring. By contrast, 24-h urinary phenylacetylglutamine and morning spot urine phenylacetylglutamine correlate strongly with dose and appear to be clin. useful non-invasive biomarkers for compliance and therapeutic monitoring.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2012:1307575 CAPLUS

TITLE: Recurrent unexplained hyperammonemia in an adolescent with arginase deficiency

AUTHOR(S): Zhang, Yan; Landau, Yuval E.; Miller, David T.; Marsden, Deborah; Berry, Gerard T.; Kellogg, Mark D.

CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, USA

SOURCE: Clinical Biochemistry (2012), 45(18), 1583-1586
CODEN: CLBIAS; ISSN: 0009-9120

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB This report investigates the etiol. of recurrent episodic elevations in plasma ammonia in an adolescent male with arginase deficiency as there were concerns regarding pre-anal. and anal. perturbations of ammonia measurements. There were repeated discrepancies between the magnitude of his ammonia levels and the severity of his clin. signs of hyperammonemia.The patient is a fourteen-year-old arginase-deficient male diagnosed at three years of age. Since 2008 (when he reached 10 years of age), there appeared to be an increase in the frequency of hospitalizations with elevated ammonia. A typical emergency visit with initial ammonia of 105 μmol/L (reference interval: 16-47 μmol/L) is illustrated. Pre-anal. and anal. procedures for the patient's sample handling were retrospectively examd.His ammonia levels were compiled since diagnosis. The frequency of his initial or peak ammonia levels greater than two times (94 μmol/L) or four times (188 μmol/L) the upper limit of normal was computed. Student t-test was used to calculate the significance of the differences before 2008 and since 2008.One out of eleven and ten out of 19 hospitalizations had initial ammonia greater than two times normal before and after 2008, resp. Both the patient's overall ammonia and peak ammonia levels are significantly higher since 2008 (p value < 0.001 for both) than those before 2008.To our knowledge, few adolescent males with arginase deficiency experience recurrent episodes of hyperammonemia requiring i.v. nitrogen scavenging agents. We hope that this study provides new insights into the natural history of arginase deficiency and the management of such patients.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2012:661267 CAPLUS

TITLE: Argininosuccinate lyase deficiency

AUTHOR(S): Nagamani, Sandesh C. S.; Erez, Ayelet; Lee, Brendan

CORPORATE SOURCE: Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

SOURCE: Genetics in Medicine (2012), 14(5), 501-507
CODEN: GEMEF3; ISSN: 1098-3600

PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB The urea cycle consists of six consecutive enzymic reactions that convert waste nitrogen into urea. Deficiencies of any of these enzymes of the cycle result in urea cycle disorders (UCDs), a group of inborn errors of hepatic metabolism that often result in life-threatening hyperammonemia. Argininosuccinate lyase (ASL) catalyzes the fourth reaction in this cycle, resulting in the breakdown of argininosuccinic acid to arginine and fumarate. ASL deficiency (ASLD) is the second most common UCD, with a prevalence of .apprx.1 in 70,000 live births. ASLD can manifest as either a severe neonatal-onset form with hyperammonemia within the first few days after birth or as a late-onset form with episodic hyperammonemia and/or long-term complications that include liver dysfunction, neurocognitive deficits, and hypertension. These long-term complications can occur in the absence of hyperammonemic episodes, implying that ASL has functions outside of its role in ureagenesis and the tissue-specific lack of ASL may be responsible for these manifestations. The biochem. diagnosis of ASLD is typically established with elevation of plasma citrulline together with elevated argininosuccinic acid in the plasma or urine. Mol. genetic testing of ASL and assay of ASL enzyme activity are helpful when the biochem. findings are equivocal. However, there is no correlation between the genotype or enzyme activity and clin. outcome. Treatment of acute metabolic decompensations with hyperammonemia involves discontinuing oral protein intake, supplementing oral intake with i.v. lipids and/or glucose, and use of i.v. arginine and nitrogen-scavenging therapy. Dietary restriction of protein and dietary supplementation with arginine are the mainstays in long-term management. Orthotopic liver transplantation (OLT) is best considered only in patients with recurrent hyperammonemia or metabolic decompensations resistant to conventional medical therapy. Genet Med 2012:14(5):501-507 Genetics in Medicine (2012); 14 5, 501-507. doi:10.1038/gim.2011.1.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:126202 CAPLUS
DOCUMENT NUMBER: 156:194959
TITLE: Dosing and monitoring patients on nitrogen-scavenging drugs
INVENTOR(S): Scharschmidt, Bruce
PATENT ASSIGNEE(S): Ucyclyd Pharma, Inc, USA
SOURCE: U.S. Pat. Appl. Publ., 48pp., Cont.-in-part of Appl. No. PCT/US2009/030362.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20120022157	A1	20120126	US 2011-61509	20110615
WO 2009134460	A1	20091105	WO 2009-US30362	20090107

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ,

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US 20100008859	A1	20100114	US 2009-350111	20090107
WO 2010025303	A1	20100304	WO 2009-US55256	20090827
WO 2010025303	A9	20100624		

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.:	US 2008-93234P	P 20080829
	US 2009-350111	A2 20090107
	WO 2009-US30362	A2 20090107
	WO 2009-US55256	W 20090827
	US 2008-48830P	P 20080429

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention provides a method for determining a dose and dosing schedule, and making dose adjustments of patients taking phenylbutyric acid (PBA) prodrugs as nitrogen scavengers to treat nitrogen retention states, including ammonia accumulation disorders as well as chronic renal failure, by measuring urinary excretion of phenylacetylglutamine and/or total urinary nitrogen. The invention provides methods to select an appropriate dosage of a PBA prodrug based on the patient's dietary protein intake, or based on previous treatments administered to the patient. The methods are applicable to selecting or modifying a dosing regimen for a subject receiving an orally administered waste nitrogen scavenging drug, and to monitoring patients receiving such drugs.

L2 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER:	2012:47116 CAPLUS
DOCUMENT NUMBER:	157:433552
TITLE:	Amino acid metabolism in patients with propionic acidaemia
AUTHOR(S):	Scholl-Buergi, Sabine; Sass, Joern Oliver; Zschocke, Johannes; Karall, Daniela
CORPORATE SOURCE:	Department of Paediatrics IV, Division of Neonatology, Neuropaediatrics and Inherited Metabolic Disorders, Innsbruck Medical University, Innsbruck, 6020, Austria
SOURCE:	Journal of Inherited Metabolic Disease (2012), 35(1), 65-70 CODEN: JIMDDP; ISSN: 0141-8955
PUBLISHER:	Springer
DOCUMENT TYPE:	Journal; General Review; (online computer file)
LANGUAGE:	English

AB A review. Propionic acidemia (PA) is an inborn error of intermediary metabolism caused by deficiency of propionyl-CoA carboxylase. The metabolic block leads to a profound failure of central metabolic pathways, including the urea and the citric acid cycles. This review will focus on changes in amino acid metabolism in this inborn disorder of metabolism The first noted disturbance of amino acid metabolism was hyperglycinemia, which is detectable in nearly all PA patients. Addnl., hyperlysinemia is a common

observation. In contrast, concns. of branched chain amino acids, especially of isoleucine, are frequently reported as decreased. These non-proportional changes of branched-chain amino acids (BCAAs) compared with aromatic amino acids are also reflected by the Fischer's ratio (concentration ratio of BCAAs to aromatic amino acids), which is decreased in PA patients. As restricted dietary intake of valine and isoleucine as precursors of propionyl-CoA is part of the standard treatment in PA, decreased plasma concns. of BCAAs may be a side effect of treatment. The concentration changes of the nitrogen scavenger glutamine have to be interpreted in the light of ammonia levels. In contrast to other hyperammonemic syndromes, in PA plasma glutamine concns. do not increase in hyperammonemia, whereas CSF glutamine concns. are elevated. Despite lactic acidemia in PA patients, hyperalaninemia is only rarely reported. The mechanisms underlying the observed changes in amino acid metabolism have not yet been elucidated, but most of the changes can be at least partly interpreted as consequence of disturbance of anaplerosis.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:397345 CAPLUS
DOCUMENT NUMBER: 155:453598
TITLE: Lysinuric protein intolerance: reviewing concepts on a multisystem disease
AUTHOR(S): Sebastio, Gianfranco; Sperandeo, Maria P.; Andria, Generoso
CORPORATE SOURCE: Department of Clinical Pediatrics, Federico II University of Naples, Italy
SOURCE: American Journal of Medical Genetics, Part C: Seminars in Medical Genetics (2011), 157(1), 54-62
CODEN: AJMGFC; ISSN: 1552-4868
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Lysinuric protein intolerance (LPI) is an inherited aminoaciduria caused by defective cationic amino acid transport at the basolateral membrane of epithelial cells in intestine and kidney. LPI is caused by mutations in the SLC7A7 gene, which encodes the y+LAT-1 protein, the catalytic light chain subunit of a complex belonging to the heterodimeric amino acid transporter family. LPI was initially described in Finland, but has worldwide distribution. Typically, symptoms begin after weaning with refusal of feeding, vomiting, and consequent failure to thrive. Hepatosplenomegaly, hematol. anomalies, neurol. involvement, including hyperammonemic coma are recurrent clin. features. Two major complications, pulmonary alveolar proteinosis and renal disease are increasingly observed in LPI patients. There is extreme variability in the clin. presentation even within individual families, frequently leading to misdiagnosis or delayed diagnosis. This condition is diagnosed by urine amino acids, showing markedly elevated excretion of lysine and other dibasic amino acids despite low plasma levels of lysine, ornithine, and arginine. The biochem. diagnosis can be uncertain, requiring confirmation by DNA testing. So far, approx. 50 different mutations have been identified in the SLC7A7 gene in a group of 142 patients from 110 independent families. No genotype-phenotype correlation could be established. Therapy requires a low protein diet, low-dose citrulline supplementation, nitrogen-scavenging compds. to prevent hyper-ammonemia, lysine, and carnitine supplements. Supportive therapy is available for most complications with bronchoalveolar lavage being necessary for alveolar proteinosis.
OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD

(8 CITINGS)
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:708850 CAPLUS
DOCUMENT NUMBER: 154:477123
TITLE: Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: Safety, pharmacokinetics and ammonia control
AUTHOR(S): Lee, Brendan; Rhead, William; Diaz, George A.; Scharschmidt, Bruce F.; Mian, Asad; Shchelochkov, Oleg; Marier, J. F.; Beliveau, Martin; Mauney, Joseph; Dickinson, Klara; Martinez, Antonia; Gargosky, Sharron; Mokhtarani, Masoud; Berry, Susan A.
CORPORATE SOURCE: Baylor College of Medicine, Houston, TX, R814, USA
SOURCE: Molecular Genetics and Metabolism (2010), 100(3), 221-228
CODEN: MGMEFF; ISSN: 1096-7192
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glycerol phenylbutyrate (glyceryl tri (4-phenylbutyrate)) (GPB) is being studied as an alternative to sodium phenylbutyrate (NaPBA) for the treatment of urea cycle disorders (UCDs). This phase 2 study explored the hypothesis that GPB offers similar safety and ammonia control as NaPBA, which is currently approved as adjunctive therapy in the chronic management of UCDs, and examined correlates of 24-h blood ammonia. Methods: An open-label, fixed sequence switch-over study was conducted in adult UCD patients taking maintenance NaPBA. Blood ammonia and blood and urine metabolites were compared after 7 days (steady state) of TID dosing on either drug, both dosed to deliver the same amount of phenylbutyric acid (PBA). Results: Ten subjects completed the study. Adverse events were comparable for the two drugs; 2 subjects experienced hyperammonemic events on NaPBA while none occurred on GPB. Ammonia values on GPB were .apprx.30% lower than on NaPBA (time-normalized AUC = 26.2 vs. 38.4 μmol/L; Cmax = 56.3 vs. 79.1 μmol/L; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time-normalized AUC) by post hoc anal. Systemic exposure (AUC0-24) to PBA on GPB was 27% lower than on NaPBA (540 vs. 739 μg h/mL), whereas exposure to phenylacetic acid (PAA) (575 vs. 596 μg h/mL) and phenylacetylglutamine (PAGN) (1098 vs. 1133 μg h/mL) were similar. Urinary PAGN excretion accounted for .apprx.54% of PBA administered for both NaPBA and GPB; other metabolites accounted for <1%. Intact GPB was generally undetectable in blood and urine. Blood ammonia correlated strongly and inversely with urinary PAGN ($r = -0.82$; $p < 0.0001$) but weakly or not at all with blood metabolite levels. Conclusions: Safety and ammonia control with GPB appear at least equal to NaPBA. Urinary PAGN, which is stoichiometrically related to nitrogen scavenging, may be a useful biomarker for both dose selection and adjustment for optimal control of venous ammonia.
OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:275617 CAPLUS
DOCUMENT NUMBER: 152:279601
TITLE: Dosing and monitoring patients on nitrogen-scavenging drugs

INVENTOR(S): Scharschmidt, Bruce
PATENT ASSIGNEE(S): Hyperion Therapeutics, USA
SOURCE: PCT Int. Appl., 99pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010025303	A1	20100304	WO 2009-US55256	20090827
WO 2010025303	A9	20100624		
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
WO 2009134460	A1	20091105	WO 2009-US30362	20090107
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US 20100008859	A1	20100114	US 2009-350111	20090107
CA 2735234	A1	20100304	CA 2009-2735234	20090827
GB 2465250	A	20100519	GB 2009-15545	20090827
GB 2465250	B	20110126		
EP 2338050	A1	20110629	EP 2009-748559	20090827
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS				
JP 2012501451	T	20120119	JP 2011-525214	20090827
US 20120022157	A1	20120126	US 2011-61509	20110615

PRIORITY APPLN. INFO.:

US 2008-93234P	P	20080829
US 2009-350111	A	20090107
WO 2009-US30362	A	20090107
US 2008-48830P	P	20080429
WO 2009-US55256	W	20090827

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention provides a method for determining a dose and dosing schedule, and making dose adjustments of patients taking phenylbutyric acid (PBA) prodrugs as nitrogen scavengers to treat nitrogen retention states, including ammonia accumulation disorders as well as chronic renal failure, by measuring urinary excretion of phenylacetylglutamine and/or total urinary nitrogen. The invention provides methods to select an appropriate dosage of a PBA prodrug based on the patient's dietary protein intake, or based on previous treatments administered to the patient. The

methods are applicable to selecting or modifying a dosing regimen for a subject receiving an orally administered waste nitrogen scavenging drug, and to monitoring patients receiving such drugs.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 1999:106789 CAPLUS
DOCUMENT NUMBER: 130:295089
TITLE: Blood levels of ammonia and nitrogen scavenging amino acids in patients with inherited hyperammonemia
AUTHOR(S): Tuchman, Mendel; Yudkoff, Marc
CORPORATE SOURCE: Departments of Pediatrics and Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Molecular Genetics and Metabolism (1999), 66(1), 10-15
CODEN: MGMEFF; ISSN: 1096-7192
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Plasma levels of glutamine (456 detns.), alanine (434 detns.), and asparagine (431 detns.) and corresponding ammonia levels (260 detns.) were retrospectively analyzed in 30 patients with hyperammonemia secondary to urea cycle disorders (including 3 patients with amino acid transport defects) and 5 patients with propionic acidemia (PA). All patients had elevated glutamine levels on one or more testing except for 2 patients with severe PA and 1 patient with a mild urea cycle disorder. All but 4 patients with urea cycle disorders showed a maximal glutamine level higher than 100 μmol/dL, and 3 patients had a maximal glutamine level of higher than 200 μmol/dL. The only exceptions were 2 asymptomatic ornithine transcarbamylase (OTC)-deficient females, 1 male with mild OTC deficiency, and 1 patient with citrullinemia (CIT) whose plasma glutamine levels were never above 100 μmol/L. Patients with CIT and argininosuccinic aciduria (ASA) showed statistically significantly lower levels of glutamine than patients with other urea cycle disorders. However, the maximal glutamine level did not directly correlate with severity of the disorder and within disorders correlated inversely with severity of outcome. Patients with PA showed statistically significant lower glutamine, alanine, and asparagine levels than patients with urea cycle disorders and the severity of this disorder correlated inversely with plasma glutamine levels. Plasma ammonia levels showed a pos. correlation with glutamine in patients with carbamyl phosphate synthetase I and OTC deficiency and a neg. correlation in patients with PA. Although, most patients also showed elevated levels of alanine and asparagine, their levels generally did not show a good correlation with glutamine (R2 = 0.25 and 0.34, resp.). (c) 1999 Academic Press.
OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 1991:477732 CAPLUS
DOCUMENT NUMBER: 115:77732
ORIGINAL REFERENCE NO.: 115:13291a,13294a
TITLE: Scavenging ratios and deposition of sulfur, nitrogen and chlorine species in eastern England
AUTHOR(S): Harrison, Roy M.; Allen, Andrew G.
CORPORATE SOURCE: Inst. Aerosol Sci., Univ. Essex, Colchester, CO4 3SQ, UK
SOURCE: Atmospheric Environment, Part A: General Topics (1991), 25A(8), 1719-23

CODEN: AEATEN; ISSN: 0960-1686
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Measurements of wet-deposited NH4+, SO42-, NO3-, and Cl-, as well as airborne concns. of these species and gaseous HNO3, HCl, and NH3, were made at a site in eastern England. Scavenging ratios based solely upon aerosol-associated species and upon aerosol plus gaseous airborne species are presented and compared with literature values. It appears that HCl and HNO3 have only a rather minor influence upon wet deposition at this site. Gaseous NH3 influences ground-level air chemical appreciably, but scavenging ratios for NH4+ are low, even when based upon aerosol NH4+ concns. alone, presumably due to altitudinal gradients in this species. The problems inherent in interpretation of scavenging ratios are discussed. Deposition of nitrogen in various chemical forms is estimated from rainwater and air composition
If a transport-limited deposition velocity is assumed for ammonia gas, dry deposition of this species accounts for around 40% of total nitrogen deposition to the ground.
OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)

L2 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 1989:54293 CAPLUS
DOCUMENT NUMBER: 110:54293
ORIGINAL REFERENCE NO.: 110:8913a,8916a
TITLE: Occurrence of effective nitrogen-scavenging bacteria in the rhizosphere of kallar grass
AUTHOR(S): Hurek, T.; Reinhold, Barbara; Grimm, B.; Fendrik, I.; Niemann, E. G.
CORPORATE SOURCE: Inst. Biophys., Univ. Hannover, Hannover, D-3000/21, Fed. Rep. Ger.
SOURCE: Plant and Soil (1988), 110(2), 339-48
CODEN: PLSOA2; ISSN: 0032-079X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bacteria occurring in high nos. on the rhizoplane of kallar grass grown at a natural site in Pakistan were effective scavengers of traces of combined N from the atmospheric Bacteria grew under appropriate conditions in N-free semi-solid malate medium in the form of a typical subsurface pellicle which resulted in a significant N gain in the medium within 3-4 days of incubation; this could be also measured by 15N-dilution Bacteria grew and incorporated N under an atmospheric containing NH3 and N2O. A rapid and strong binding of strain W1 to roots of kallar grass grown in hydroponic culture was found by using a 32P-tracer technique. There was no evidence for diazotrophy because the bacteria failed to grow on N-free media when gases of high purity were used. No 15N2 was incorporated when bacteria were grown on 15N2, although a N gain was found, no acetylene reduction was observed,
and no homol. with DNA containing sequences of nifHDK structural genes for the nitrogenase components from Klebsiella pneumoniae were detected. Owing to close contact of these bacteria with roots of kallar grass, utilization of scavenged N by the plant may have to be taken into account.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

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(FILE 'HOME' ENTERED AT 20:33:38 ON 20 DEC 2012)

FILE 'CAPLUS' ENTERED AT 20:33:50 ON 20 DEC 2012
L1 40 S "NITROGEN SCAVENGER" OR "NITROGEN SCAVENGING"

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L2            11 S L1 AND AMMONIA

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 NEWS  2  JAN 11  STN Express 8.6 Now Available
 NEWS  3  MAR 23  Enhanced Coverage of Latin America (AR, MX) in Derwent World
                  Patent Index
 NEWS  4  APR 15  USPATFULL/USPAT2 Now Include Corporate Patent Applicant
                  Information
 NEWS  5  MAY 22  Country Coverage in Derwent World Patent Index Extended to
                  Include Turkey
 NEWS  6  MAY 28  Partner with CAS to help shape the future of CAS products!
 NEWS  7  JUL 2   Major Update to GBFULL Improves Quality of Full Text
 NEWS  8  JUL 7   100 Millionth Small Molecule Added to CAS REGISTRY
 NEWS  9  SEP 15  New Version of Emtree Introduces over 800 New Terms to
                  Embase on Classic STN and New STN
 NEWS 10  NOV 25  Change to PI field in CAplus records
 NEWS 11  DEC 17  Latest Release of New STN Enhances Search Functionality,
                  Workflow, and Efficiency
 NEWS 12  JAN 11  PatentPak Now available to STN Express 8.6 and STN on the
                  Web customers
 NEWS 13  JAN 11  CAplus Family of Files Updated with New Data to Support
                  PatentPak in STN
 NEWS 14  JAN 14  The Derwent World Patents Index (DWPI): Latest Manual Code
                  Revision is now live

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              AND CURRENT DISCOVER FILE IS DATED 11 JAN 2016.

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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       6.75       6.75

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FILE COVERS 1907 - 1 Feb 2016 VOL 164 ISS 7
FILE LAST UPDATED: 31 Jan 2016 (20160131/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Dec 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Dec 2015

CAplus includes complete International Patent Classification (IPC)
reclassification data for the first quarter of 2016.

CAplus now includes the comprehensive Cooperative Patent Classification
(CPC).  See HELP CPC for details.

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s "glyceryl tri-[P-phenylbutyrate]"
         27025 "GLYCERYL"
             2 "GLYCERYLS"
         27026 "GLYCERYL"
                 ("GLYCERYL" OR "GLYCERYLS")
        177002 "TRI"
        189468 "TRIS"
        356204 "TRI"
                 ("TRI" OR "TRIS")
       3919888 "P"
          1663 "PHENYLBUTYRATE"
            37 "PHENYLBUTYRATES"
          1682 "PHENYLBUTYRATE"
                 ("PHENYLBUTYRATE" OR "PHENYLBUTYRATES")
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             2 "GLYCERYLS"
         27026 "GLYCERYL"
                 ("GLYCERYL" OR "GLYCERYLS")
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L2           3 "GLYCERYL TRI-[4-PHENYLBUTYRATE]"
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=> d l2 1-3 ibib ab

L2   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2016 ACS on STN
ACCESSION NUMBER:        2013:875590  CAPLUS
DOCUMENT NUMBER:         159:21380
TITLE:                   Low dose therapeutic use of glyceryl
                         tri-(4-phenylbutyrate)
INVENTOR(S):             Truog, Peter; Buschmann, Helmut H.
PATENT ASSIGNEE(S):      LUNAMeD AG, Switz.
SOURCE:                  Eur. Pat. Appl., 16pp.; Chemical Indexing Equivalent
                         to 159:21379 (WO)
                         CODEN: EPXXDW
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  2
PATENT INFORMATION:
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
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     EP 2599482           A1   20130605    EP 2011-9476             20111130
         R:  AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
             HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO,
             RS, SE, SI, SK, SM, TR, BA, ME
     WO 2013079205        A1   20130606    WO 2012-EP4936           20121129
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
             BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE,
             EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS,
             JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY,
             MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
             PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK,
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         RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
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             SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM
PRIORITY APPLN. INFO.:                    EP 2011-9476          A  20111130
AB   The present invention relates to the therapeutic use of Glyceryl
     tri-(4-phenylbutyrate) in the treatment of various diseases and
     disorders, such as Alzheimer's disease, cancer, depression, or cystic
     fibrosis.  Particularly, the present invention provides Glyceryl
     tri-(4-phenylbutyrate) at low daily doses for use in the treatment
     of various diseases, pharmaceutical compns. and kits comprising Glyceryl
     tri-(4-phenylbutyrate) at low doses for the treatment of various
     diseases, and methods for treatment of Alzheimer's disease involving the
     administration of Glyceryl tri-(4-phenylbutyrate) at low daily doses.

L2   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2016 ACS on STN
ACCESSION NUMBER:        2013:875588  CAPLUS
DOCUMENT NUMBER:         159:21379
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TITLE: Low dose therapeutic use of glyceryl tri-(4-phenylbutyrate)
INVENTOR(S): Truog, Peter; Buschmann, Helmut H.
PATENT ASSIGNEE(S): LUNAMeD AG, Switz.
SOURCE: PCT Int. Appl., 27pp.; Chemical Indexing Equivalent to 159:21380 (EP)
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013079205	A1	20130606	WO 2012-EP4936	20121129
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
EP 2599482	A1	20130605	EP 2011-9476	20111130
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				

PRIORITY APPLN. INFO.: EP 2011-9476 A 20111130
AB The present invention relates to the therapeutic use of Glyceryl tri-(4-phenylbutyrate) in the treatment of various diseases and disorders, such as Alzheimer's disease, cancer, depression, or cystic fibrosis. Particularly, the present invention provides Glyceryl tri-(4-phenylbutyrate) at low daily doses for use in the treatment of various diseases, pharmaceutical compns. and kits comprising Glyceryl tri-(4-phenylbutyrate) at low doses for the treatment of various diseases, and methods for treatment of Alzheimer's disease involving the administration of Glyceryl tri-(4-phenylbutyrate) at low daily doses.

L2 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2016 ACS on STN
ACCESSION NUMBER: 2010:708850 CAPLUS
DOCUMENT NUMBER: 154:477123
TITLE: Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: Safety, pharmacokinetics and ammonia control
AUTHOR(S): Lee, Brendan; Rhead, William; Diaz, George A.; Scharschmidt, Bruce F.; Mian, Asad; Shchelochkov, Oleg; Marier, J. F.; Beliveau, Martin; Mauney, Joseph; Dickinson, Klara; Martinez, Antonia; Gargosky, Sharron; Mokhtarani, Masoud; Berry, Susan A.
CORPORATE SOURCE: Baylor College of Medicine, Houston, TX, R814, USA
SOURCE: Molecular Genetics and Metabolism (2010), 100(3), 221-228
CODEN: MGMEFF; ISSN: 1096-7192
DIGITAL OBJECT ID: 10.1016/j.ymgme.2010.03.014
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glycerol phenylbutyrate (glyceryl tri (4-phenylbutyrate)) (GPB) is being studied as an alternative to sodium phenylbutyrate (NaPBA) for the treatment of urea cycle disorders (UCDs). This phase 2 study explored the hypothesis that GPB offers similar safety and ammonia control as NaPBA, which is currently approved as adjunctive therapy in the chronic management of UCDs, and examined correlates of 24-h blood ammonia. Methods: An open-label, fixed sequence switch-over study was conducted in adult UCD patients taking maintenance NaPBA. Blood ammonia and blood and urine metabolites were compared after 7 days (steady state) of TID dosing on either drug, both dosed to deliver the same amount of phenylbutyric acid (PBA). Results: Ten subjects completed the study. Adverse events were comparable for the two drugs; 2 subjects experienced hyperammonemic events on NaPBA while none occurred on GPB. Ammonia values on GPB were .apprx.30% lower than on NaPBA (time-normalized AUC = 26.2 vs. 38.4 μmol/L; Cmax = 56.3 vs. 79.1 μmol/L; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time-normalized AUC) by post hoc anal. Systemic exposure (AUC0-24) to PBA on GPB was 27% lower than on NaPBA (540 vs. 739 μg h/mL), whereas exposure to phenylacetic acid (PAA) (575 vs. 596 μg h/mL) and phenylacetylglutamine (PAGN) (1098 vs. 1133 μg h/mL) were similar. Urinary PAGN excretion accounted for .apprx.54% of PBA administered for both NaPBA and GPB; other metabolites accounted for <1%. Intact GPB was generally undetectable in blood and urine. Blood ammonia correlated strongly and inversely with urinary PAGN ($r = -0.82$; $p < 0.0001$) but weakly or not at all with blood metabolite levels. Conclusions: Safety and ammonia control with GPB appear at least equal to NaPBA. Urinary PAGN, which is stoichiometrically related to nitrogen scavenging, may be a useful biomarker for both dose selection and adjustment for optimal control of venous ammonia.
OS.CITING REF COUNT: 26 THERE ARE 26 CAPLUS RECORDS THAT CITE THIS RECORD (26 CITINGS)

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(FILE 'HOME' ENTERED AT 11:00:21 ON 01 FEB 2016)

FILE 'CAPLUS' ENTERED AT 11:15:32 ON 01 FEB 2016
L1 0 S "GLYCERYL TRI-[P-PHENYLBUTYRATE]"
L2 3 S "GLYCERYL TRI-[4-PHENYLBUTYRATE]"

=> s l2 and urea
344374 UREA
14175 UREAS
348696 UREA
(UREA OR UREAS)
L3 1 L2 AND UREA

=> d l3

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2016 ACS on STN
AN 2010:708850 CAPLUS
DN 154:477123
TI Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: Safety, pharmacokinetics and ammonia control
AU Lee, Brendan; Rhead, William; Diaz, George A.; Scharschmidt, Bruce F.; Mian, Asad; Shchelochkov, Oleg; Marier, J. F.; Beliveau, Martin; Mauney, Joseph; Dickinson, Klara; Martinez, Antonia; Gargosky, Sharron; Mokhtarani, Masoud; Berry, Susan A.
CS Baylor College of Medicine, Houston, TX, R814, USA
SO Molecular Genetics and Metabolism (2010), 100(3), 221-228

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     CODEN: MGMEFF; ISSN: 1096-7192
DOI  10.1016/j.ymgme.2010.03.014
PB   Elsevier B.V.
DT   Journal
LA   English
OSC.G   26    THERE ARE 26 CAPLUS RECORDS THAT CITE THIS RECORD (26 CITINGS)


=> d his

     (FILE 'HOME' ENTERED AT 11:00:21 ON 01 FEB 2016)

     FILE 'CAPLUS' ENTERED AT 11:15:32 ON 01 FEB 2016
L1            0 S "GLYCERYL TRI-[P-PHENYLBUTYRATE]"
L2            3 S "GLYCERYL TRI-[4-PHENYLBUTYRATE]"
L3            1 S L2 AND UREA

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BIB DATA SHEET

CONFIRMATION NO. 3046

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/958,259	12/03/2015	424	1621	HOR0026-201TC2-US

APPLICANTS
Horizon Therapeutics, Inc., Deerfield, IL;

INVENTORS
Bruce Scharschmidt, San Francisco, CA;
Masoud Mokhtarani, Walnut Creek, CA;

**** CONTINUING DATA ***************************
This application is a CON of 14/816,674 08/03/2015 PAT 9254278
which is a CON of 13/775,000 02/22/2013 PAT 9095559
which is a CON of 13/417,137 03/09/2012 PAT 8404215
which claims benefit of 61/542,100 09/30/2011
and claims benefit of 61/564,668 11/29/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
12/11/2015

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged / Savitha Rao / Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	3	10	4

ADDRESS
GLOBAL PATENT GROUP - HOR
1005 NORTH WARSON ROAD
SUITE 404
SAINT LOUIS, MO 63132
UNITED STATES

TITLE
METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

FILING FEE RECEIVED		
2440	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

BIB (Rev. 05/07).

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14958259	SCHARSCHMIDT ET AL.
	Examiner	Art Unit
	SAVITHA RAO	1621

CPC- SEARCHED		
Symbol	Date	Examiner
A61K31/216 OR G01N31/221 OR Y10T436/175383	2/1/2016	SR

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
eaST search (See attached)	2/1/2016	SR
Inventor search in EAST and PALM	2/1/2016	SR
STN search (see attached)	2/1/2016	SR
NPL search in STN and google	2/1/2016	

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/216	2/1/2016	SR
G01N	31/221	2/1/2016	SR
Y10T	436/175383	2/1/2016	SR

	/SAVITHA RAO/ Primary Examiner.Art Unit 1621

EAST Search History

EAST Search History (Prior Art)

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S3	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:46
S4	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:56
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S6	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:56
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S9	8	S7 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S10	2	S9 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S11	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR;	OR	OFF	2012/11/15 14:12

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S14	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 14:13
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S21	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 10:56
S22	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 10:56
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S29	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
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S32	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 10:56
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S39	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S40	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT;	OR	OFF	2012/12/20 16:43

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S46	2	S45 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S47	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
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S79	135	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR;	OR	OFF	2015/10/29 09:59

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S84	19	S83 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/02/01 10:51
S85	11	S84 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/02/01 10:51
S86	68	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/02/01 10:53
S87	9	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/02/01 10:54
S88	0	"US 9254278"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/02/01 11:26
S89	0	"US 9254278"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/02/01 11:26

EAST Search History (Interference)

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 21

Complete if Known	
Application Number	TBD
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First Named Inventor	Bruce Scharschmidt
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	HOR0026-201TC2-US

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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	P2	4,457,942	07-03-1984	Brusilow, S.W.	
	P3	5,654,333	08-05-1997	The United States Of America As Represented By The Department Of Health And Human Services	
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	P10	8,642,012	02-04-2014	Hyperion Therapeutics, Inc.	
	P11	9,078,865	7-14-2015	Lee	
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	P17	2010/0008859	01-14-2010	Hyperion Therapeutics, Inc.	
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	P22	2013/0281530	10-24-2013	Scharschmidt, et al	
	P23	2014/0142186	05-22-2014	Hyperion Therapeutics, Inc.	
	P24	2015/0105469	4-16-2015	Scharschmidt et al.	
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	F9	WO2013/048558	04-04-2013	Hyperion Therapeutics, Inc.		
	F10	WO2013/158145	10-24-2013	Hyperion Therapeutics, Inc.		

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	D5	ANDA Notice Letter, Lupin Ltd. to Horizon Therapeutics, Inc.. Re: Notification of Invalidity, Unenforceability, and/or Noninfringement for U.S. Patent Nos. 8,404,215 and 8,642,012 Pursuant to § 505(j)(2)(B)(ii) and (iv) of the Federal Food, Drug, and Cosmetic Act, Sept. 4, 2015	
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Sheet 5 of 21

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Sheet 15 of 21

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Application Number	TBD
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First Named Inventor	Bruce Scharschmidt
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	HOR0026-201TC2-US

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Scharscmidt *et al.* Application No.: 14/958,259 Filed: 12/03/2015 For: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	Confirmation No.: 3046 Examiner: Savitha M. Rao Art Unit: 1621

RESPONSE TO NON-FINAL ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Please enter the following amendments and remarks.

Amendments to the Claims begin on page 2.

Remarks/Arguments follow the Amendments to the Claims.

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1.-21. (Cancelled)

22. (Previously presented) A method of treating a subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level,

wherein the upper limit of normal for plasma ammonia level is in the range of 26-64 μmol/L.

23. (Previously presented) The method of claim 22, wherein the upper limit of normal for plasma ammonia level is in the range of 32-38 μmol/L.

24. (Previously presented) The method of claim 23, wherein the upper limit of normal for plasma ammonia level is in the range of 34-36 μmol/L.

25. (Cancelled)

26. (Cancelled)

27. (Cancelled)

28. (Previously presented) The method of claim 22, further comprising repeating steps (a) to (c) until the subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level.

29. (Previously presented) The method of claim 22, wherein the adjusted dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

30.-35. (Cancelled)

36. (Previously presented) A method of treating a pediatric subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the pediatric subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

37. (Previously presented) The method of claim 36, further comprising repeating steps (a) to (c) until the pediatric subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level.

38. (Previously presented) The method of claim 36, wherein the adjusted dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

39. (Previously presented) A method of treating an adult subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-

phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the adult subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

40. (Previously presented) The method of claim 39, further comprising repeating steps (a) to (c) until the adult subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level.

41. (Previously presented) The method of claim 39, wherein the adjusted dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

42. (New) A method of treating a patient having a urea cycle disorder comprising:

(a) administering an initial effective dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) to the patient, wherein the initial effective dosage is calculated based on body surface area of the patient;

(b) measuring the patient's urinary PAGN and/or fasting plasma ammonia level to determine whether to change the dosage of the glyceryl tri-[4-phenylbutyrate] (HPN-100); and

(c) administering a subsequent effective dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) to the patient that is either the same as the initial effective dosage or is an increased dosage, wherein said increased dosage, if any, is calculated based on the patient's urinary PAGN and/or fasting plasma ammonia level.

43. (New) The method of claim 42, further comprising repeating steps (b) to (c) until the subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level.

44. (New) The method of claim 42, wherein the initial effective dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

45. (New) The method of claim 42, wherein the subsequent effective dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

REMARKS

Claims 25-27 and 30-35 have been cancelled, without prejudice or disclaimer. New claims 42-45 have been added. No new matter has been added by these amendments. With the entry of this amendment, claims 22-24, 28, 29, and 36-45 are pending.

Claims 22-41 have been rejected on the ground of non-statutory double patenting over claims 2, 4 and 7-10 of U.S. Patent No. 9,245,278, claims 3-6 of U.S. Patent No. 8,404,215, claims 1-12 of U.S. Patent No. 8,642,012, and claims 1-15 of U.S. Patent No. 9,095,559. Solely to expedite prosecution and without in any way conceding to the rejection, Applicant submits terminal disclaimers over each of those patents. Applicant requests that the rejection be withdrawn.

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance and an action to that end is respectfully requested.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Director is authorized to charge any additional fees during pendency of this application, including any required extension of time fees, or credit any overpayment to Deposit Account Number 50-4297. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. § 1.136(a)(3).

February 18, 2016
Date

/Brock Levin/
Brock Levin, Reg. No. 65,040
Attorney for Applicants

Global Patent Group, LLC
1005 North Warson Road, Suite 404
St. Louis, Missouri 63132
Tele: 314-812-8020
Fax.: 314-685-2300

Electronic Acknowledgement Receipt	
EFS ID:	24946500
Application Number:	14958259
International Application Number:	
Confirmation Number:	3046
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Brock D. Levin/Vicki Truman
Filer Authorized By:	Brock D. Levin
Attorney Docket Number:	HOR0026-201TC2-US
Receipt Date:	18-FEB-2016
Filing Date:	03-DEC-2015
Time Stamp:	11:08:06
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		20160218_Response1.pdf	51991 583f4c7ca02e9fc177956432c9a14eafc669494c	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6
Warnings:			
Information:			
	Total Files Size (in bytes):	51991	

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.

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

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	14958259
Filing Date	03-Dec-2015
First Named Inventor	Bruce Scharschmidt
Attorney Docket Number	HOR0026-201TC2-US
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

☒ 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
Horizon Therapeutics, Inc.	100%

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)

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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.

Applicant 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 65040

○ 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	/Brock Levin/
Name	Brock Levin

*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:	14958259
Filing Date:	03-Dec-2015
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Brock D. Levin/Vicki Truman
Attorney Docket Number:	HOR0026-201TC2-US

Filed as Large 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	1814	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.: 14958259

Filing Date: 03-Dec-2015

Applicant/Patent under Reexamination: Scharschmidt et al.

Electronic Terminal Disclaimer filed on February 18, 2016

☒ 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:	24946661
Application Number:	14958259
International Application Number:	
Confirmation Number:	3046
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Brock D. Levin/Vicki Truman
Filer Authorized By:	Brock D. Levin
Attorney Docket Number:	HOR0026-201TC2-US
Receipt Date:	18-FEB-2016
Filing Date:	03-DEC-2015
Time Stamp:	11:17:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	11591
Deposit Account	504297
Authorized User	TRUMAN, VICKI
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	34866 a952431d7f56a62cf4ff446dfb39030e6e016f2f	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30603 1acbd7371a59916f79f59deae7e5ddb8143ae498	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	65469		

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/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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 displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/958,259	Filing Date 12/03/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	02/18/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 15	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						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 number found in the appropriate box in column 1.

LIE
/TAMIE JARRETT/

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NOTICE OF ALLOWANCE AND FEE(S) DUE

101325 7590 03/08/2016

GLOBAL PATENT GROUP - HOR
1005 NORTH WARSON ROAD
SUITE 404
SAINT LOUIS, MO 63132

EXAMINER
RAO, SAVITHA M

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 03/08/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/958,259	12/03/2015	Bruce Scharschmidt	HOR0026-201TC2-US	3046

TITLE OF INVENTION: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/08/2016

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)

101325 7590 03/08/2016
GLOBAL PATENT GROUP - HOR
1005 NORTH WARSON ROAD
SUITE 404
SAINT LOUIS, MO 63132

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.
14/958,259	12/03/2015	Bruce Scharschmidt	HOR0026-201TC2-US	3046

TITLE OF INVENTION: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/08/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1621	424-009200

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. _____

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

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/958,259	12/03/2015	Bruce Scharschmidt	HOR0026-201TC2-US	3046

101325 7590 03/08/2016

GLOBAL PATENT GROUP - HOR
1005 NORTH WARSON ROAD
SUITE 404
SAINT LOUIS, MO 63132

EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 03/08/2016

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. 14/958,259	Applicant(s) SCHARSCHMIDT ET AL.	
	Examiner SAVITHA RAO	Art Unit 1621	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 *02/18/2016*.
   ☐ 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 *22-24,28,29 and 36-45*. 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 _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SAVITHA RAO/
Primary Examiner, Art Unit 1621

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

DETAILED ACTION

Claims 22-24, 28-29 and 36-45 and are pending in the instant application.

Applicants present new claims 42-45 with their response on 02/18/2016.

The terminal disclaimer filed on 02/18/2016 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US patent nos. 9,254,278, 8,404,215, 9,095,559 and 8,642,012 has been reviewed and is accepted. The terminal disclaimer has been recorded.

REASONS FOR ALLOWANCE

In view of the applicants arguments filed on 1 and terminal disclaimer filed on 02/18/2016 and the following examiners statement of reasons for allowance, claims 22-24, 28-29 and 36-41 are found to be allowable. Upon further review, new claims 42-45 are also found to free of art and do not consist of any 112 issues and are supported in the original specification. Accordingly, new claims 42-45 are also found to be allowable along with originally presented claims.

Following a diligent search it was determined that the prior art neither teaches nor provides adequate motivation to arrive at the instantly claimed 22. (Previously presented) A method of treating a subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who

has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising: (a) measuring a fasting plasma ammonia level for the subject; (b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and (c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level, wherein the upper limit of normal for plasma ammonia level is in the range of 26-64 pmol/L.

Conclusion

Claims 22-24, 28-29 and 36-45 (renumbered 1-15) are allowed.

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 SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Melanie McCormick can be reached at 571-272-8037. 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.

/SAVITHA RAO/

Primary Examiner, Art Unit 1621

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	0	"13417137".rlan. or ("13".src. and "417137".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 13:46
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S3	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:46
S4	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:56
S5	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:56
S6	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:56
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S9	8	S7 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S10	2	S9 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S11	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR;	OR	OFF	2012/11/15 14:12

			DERWENT			
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S29	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
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S40	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT;	OR	OFF	2012/12/20 16:43

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S64	2	S63 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S65	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
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S72	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
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S74	64	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/10/28 17:33
S75	29	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/10/28 17:33
S76	51	("20030195255" | "20050273359" | "20080119554" | "20100008859" | "20100016207" | "20120022157" | "20130210914" | "20130281530" | "20140142186" | "4457942" | "5654333" | "6219567" | "8094521" | "8404215" | "8642012" | "9078865").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/10/29 09:56
S77	2	"US 9095559"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/10/29 09:57
S78	4	"US 8404215"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/10/29 09:57
S79	135	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR;	OR	OFF	2015/10/29 09:59

			DERWENT			
S80	11	S76 and S79	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/10/29 09:59
S81	4	"US 8642012"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/10/29 10:02
S82	0	"14958259".rlan. or ("14".src. and "958259".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/02/01 10:31
S83	25	("20030195255" | "20040229948" | "20050273359" | "20060135612" | "20080119554" | "20100008859" | "20100016207" | "20120022157" | "20120220661" | "20130210914" | "20130281530" | "20140142186" | "20150094278" | "20150105469" | "4284647" | "4457942" | "5654333" | "5968979" | "6060510" | "6083984" | "6219567" | "8094521" | "8404215" | "8642012" | "9078865").PN.	US-PGPUB; USPAT	OR	OFF	2016/02/01 10:51
S84	19	S83 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/02/01 10:51
S85	11	S84 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/02/01 10:51
S86	68	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/02/01 10:53
S87	9	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/02/01 10:54
S88	0	"US 9254278"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/02/01 11:26
S89	0	"US 9254278"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/02/01 11:26
S90	6	"13417137".rlan. or ("13".src. and "417137".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S91	16	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S92	10	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT;	OR	OFF	2016/03/02 10:39

			USOCR			
S93	70	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S94	10	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S95	35	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S96	25	("20040229948" | "20060135612" | "4284647" | "6083984" | "20080119554" | "6219567" | "20100008859" | "6050510" | "5968979" | "20100008859" | "6219567").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S97	6	S90 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S98	8	S96 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S99	2	S98 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S100	139	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S101	18	S100 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S102	16	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S103	70	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S104	18	("4284647" | "6083984" | "6050510" | "6219567" | "20040229948" | "20080119554" | "20060135612" | "5968979" | "20100008859").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39

S105	2	S104 and "nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S106	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2016/03/02 10:39
S107	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S108	6	"13417137".rlan. or ("13".src. and "417137".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S109	16	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S110	10	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S111	70	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S112	10	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S113	35	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S114	25	("20040229948" | "20060135612" | "4284647" | "6083984" | "20080119554" | "6219567" | "20100008859" | "6050510" | "5968979" | "20100008859" | "6219567").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S115	6	S108 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S116	8	S114 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S117	2	S116 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S118	139	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39

S119	18	S118 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S120	16	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S121	70	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S122	18	("4284647" | "6083984" | "6050510" | "6219567" | "20040229948" | "20080119554" | "20060135612" | "5968979" | "20100008859").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S123	2	S122 and "nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S124	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2016/03/02 10:39
S125	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S126	6	"13417137".rlan. or ("13".src. and "417137".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S127	16	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S128	10	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S129	70	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S130	10	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S131	35	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S132	25	("20040229948" | "20060135612" | "4284647" | "6083984" | "20080119554" | "6219567" | "20100008859" | "6050510" | "5968979" | "20100008859" | "6219567").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO;	OR	OFF	2016/03/02 10:39

			DERWENT; IBM_TDB			
S133	6	S126 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S134	8	S132 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S135	2	S134 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S136	139	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S137	18	S136 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S138	16	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S139	70	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S140	18	("4284647" | "6083984" | "6050510" | "6219567" | "20040229948" | "20080119554" | "20060135612" | "5968979" | "20100008859").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S141	2	S140 and "nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S142	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2016/03/02 10:39
S143	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S144	6	"13417137".rlan. or ("13".src. and "417137".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S145	16	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S146	10	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S147	70	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR;	OR	OFF	2016/03/02 10:39

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S148	10	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S149	35	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S150	25	("20040229948" | "20060135612" | "4284647" | "6083984" | "20080119554" | "6219567" | "20100008859" | "6050510" | "5968979" | "20100008859" | "6219567").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S151	6	S144 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S152	8	S150 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S153	2	S152 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S154	139	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S155	18	S154 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S156	16	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S157	70	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S158	18	("4284647" | "6083984" | "6050510" | "6219567" | "20040229948" | "20080119554" | "20060135612" | "5968979" | "20100008859").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S159	2	S158 and "nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39

S160	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2016/03/02 10:39
S161	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S162	2	"14816674".rlan. or ("14".src. and "816674".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S163	70	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S164	35	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S165	51	("20030195255" | "20050273359" | "20080119554" | "20100008859" | "20100016207" | "20120022157" | "20130210914" | "20130281530" | "20140142186" | "4457942" | "5654333" | "6219567" | "8094521" | "8404215" | "8642012" | "9078865").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S166	4	"US 9095559"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S167	6	"US 8404215"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S168	139	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S169	11	S165 and S168	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S170	5	"US 8642012"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S171	0	"14958259".rlan. or ("14".src. and "958259".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S172	25	("20030195255" | "20040229948" | "20050273359" | "20060135612" | "20080119554" | "20100008859" | "20100016207" | "20120022157" | "20120220661" | "20130210914" | "20130281530" | "20140142186" |	US-PGPUB; USPAT	OR	OFF	2016/03/02 10:39

		"20150094278" | "20150105469" | "4284647" | "4457942" | "5654333" | "5968979" | "6060510" | "6083984" | "6219567" | "8094521" | "8404215" | "8642012" | "9078865").PN.				
S173	19	S172 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S174	11	S173 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S175	70	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/03/02 10:39
S176	10	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/02 10:39
S177	2	"US 9254278"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S178	2	"US 9254278"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 10:39
S179	0	"14958259".rlan. or ("14".src. and "958259".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 11:17
S180	2	"14816674".rlan. or ("14".src. and "816674".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 11:19
S181	4	"13775000".rlan. or ("13".src. and "775000".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 11:19
S182	6419	((A61K31/216 OR A61K9/0053 OR G01N2800/085 OR G01N31/221 OR G01N33/4925 OR Y10T436/175383).CPC.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 11:20
S183	1795	S182 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 11:41
S184	84	S183 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 11:42
S185	14	S184 and "urea cycle"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2016/03/02 11:42

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S186	4590	((A61K31/216 OR A61K9/0053 OR G01N2800/085 OR G01N31/221 OR G01N33/4925 OR Y10T436/175383).CPC.)	US-PGPUB; USPAT	OR	OFF	2016/03/02 11:42
S187	1707	S186 and nitrogen	US-PGPUB; USPAT	OR	OFF	2016/03/02 11:42
S188	82	S187 and scavenging	US-PGPUB; USPAT	OR	OFF	2016/03/02 11:42
S189	12	S188 and "urea cycle"	US-PGPUB; USPAT	OR	OFF	2016/03/02 11:43

3/2/2016 12:39:24 PM
H:\ EAST - WKSP\ Workspaces\ 14 applications\ 14958259.wsp

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14958259	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SAVITHA RAO	1621

CPC						
Symbol					**Type**	**Version**
A61K		31	/	235	F	2013-01-01
A61K		9	/	0053	I	2013-01-01
			/			
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CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	15	
/SAVITHA RAO/ Primary Examiner.Art Unit 1621	03/02/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14958259	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SAVITHA RAO	1621

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
		A	6	1	K	49 / 00 (2006.01.01)						
CROSS REFERENCE(S)		A	6	1	P	13 / 00 (2006.0)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											

NONE (Assistant Examiner) (Date)		**Total Claims Allowed:** 15	
/SAVITHA RAO/ Primary Examiner.Art Unit 1621 (Primary Examiner)	03/02/2016 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14958259	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SAVITHA RAO	1621

☒ 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

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 15	
/SAVITHA RAO/ Primary Examiner.Art Unit 1621 (Primary Examiner)	03/02/2016 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

U.S. Patent and Trademark Office Part of Paper No. 20160302

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14958259	SCHARSCHMIDT ET AL.
	Examiner	Art Unit
	SAVITHA RAO	1621

CPC- SEARCHED		
Symbol	Date	Examiner
A61K31/216 OR G01N31/221 OR Y10T436/175383	3/2/2016	SR

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
eaST search (See attached)	2/1/2016	SR
Inventor search in EAST and PALM	2/1/2016	SR
STN search (see attached)	2/1/2016	SR
NPL search in STN and google	2/1/2016	SR
updated EAST search (see attached)	3/2/2016	SR
updated inventor search in EAST and PALM	3/2/2016	SR
reviewed previous STN search and STn searches of parent applications	3/2/2016	SR

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/216	3/2/2016	SR
G01N	31/221	3/2/2016	SR
Y10T	436/175383	3/2/2016	SR

	/SAVITHA RAO/ Primary Examiner.Art Unit 1621

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/958,259	12/03/2015	Bruce Scharschmidt	HOR0026-201TC2-US

CONFIRMATION NO. 3046

101325
GLOBAL PATENT GROUP - HOR
1005 NORTH WARSON ROAD
SUITE 404
SAINT LOUIS, MO 63132

PUBLICATION NOTICE

OC000000081672587

Title:METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

Publication No.US-2016-0081969-A1
Publication Date:03/24/2016

NOTICE OF PUBLICATION OF APPLICATION

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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101325 7590 03/08/2016
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(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/958,259	12/03/2015	Bruce Scharschmidt	HOR0026-201TC2-US	3046

TITLE OF INVENTION: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/08/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1621	424-009200

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
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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: Horizon Therapeutics, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Lake Forest, IL

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

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Authorized Signature /Brock Levin/ Date March 28, 2016

Typed or printed name Brock Levin Registration No. 65,040

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:	14958259
Filing Date:	03-Dec-2015
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Brock D. Levin/Valerie Lechner
Attorney Docket Number:	HOR0026-201TC2-US

Filed as Large 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	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt	
EFS ID:	25323807
Application Number:	14958259
International Application Number:	
Confirmation Number:	3046
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Brock D. Levin/Valerie Lechner
Filer Authorized By:	Brock D. Levin
Attorney Docket Number:	HOR0026-201TC2-US
Receipt Date:	28-MAR-2016
Filing Date:	03-DEC-2015
Time Stamp:	18:09:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$960
RAM confirmation Number	4514
Deposit Account	504297
Authorized User	LECHNER, VALERIE
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)	

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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)	20160328_Issue_fee_transmittal.pdf	88937 c9e2d047b0afd7492e6d3f5a573f19dc09c44ed5	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30820 3ef7b114978bf729e0626ed043079fc610c9b25a	no	2
Warnings:					
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		Total Files Size (in bytes):	119757		

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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
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PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 21

Complete if Known	
Application Number	TBD
Filing Date	TBD
First Named Inventor	Bruce Scharschmidt
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	HOR0026-201TC2-US

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
	P1	4,284,647	08-18-1981	~~The Johns Hopkins University~~	Brusilow et al.
	P2	4,457,942	07-03-1984	Brusilow, S.W.	
	P3	5,654,333	08-05-1997	The United States ~~Of America As Represented By The Department Of Health And Human Services~~	Samid
	P4	5,968,979	10-19-1999	Brusilow ~~Enterprises Llc~~	
	P5	6,060,510	05-09-2000	Brusilow ~~Enterprises Llc~~	
	P6	6,083,984	07-04-2000	Brusilow ~~Enterprises Llc~~	
	P7	6,219,567	04-17-2001	~~Cardiox Corporation~~	Eggers et al.
	P8	8,094,521	01-10-2012	~~Nightengale Products LLC~~	Levy
	P9	8,404,215	03-26-2013	~~Hyperion Therapeutics, Inc.~~	Scharschmidt et al.
	P10	8,642,012	02-04-2014	~~Hyperion Therapeutics, Inc.~~	Scharschmidt
	P11	9,078,865	7-14-2015	Lee	
	P12	2003/0195255	10-16-2003	Marshall L. Summar	
	P13	2004/0229948	11-18-2004	Marshall L. Summar et al	
	P14	2005/0273359	12-08-2005	Young, D.E.	
	P15	2006/0135612	06-22-2006	U.S. Department ~~Of Veterans Affairs~~	Ferrante
	P16	2008/0119554	05-22-2008	Rajiv Jalan et al	
	P17	2010/0008859	01-14-2010	~~Hyperion Therapeutics, Inc.~~	Scharschmidt
	P18	2010/0016207	01-21-2010	Wurtman, RJ et al	
	P19	2012/0022157	01-26-2012	~~Ucyclyd Pharma, Inc~~	Scharschmidt
	P20	2012/0220661	08-30-2012	~~Baylor College of Medicine~~	Lee
	P21	2013/0210914	08-15-2013	~~Hyperion Therapeutics, Inc.~~	Scharschmidt et al.
	P22	2013/0281530	10-24-2013	Scharschmidt, et al	
	P23	2014/0142186	05-22-2014	~~Hyperion Therapeutics, Inc.~~	Scharschmidt et al.
	P24	2015/0105469	4-16-2015	Scharschmidt et al.	
	P25	2015/0094278	~~3-26-15~~ 04/2015	Scharschmidt et al.	

Change(s) applied to document, /N.D.W./ 3/10/2016

Change(s) applied to document, /N.D.W./ 3/10/2016

Change(s) applied to document, /S.H./ 4/5/2016

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.

4835-0776-7055.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.R/

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/958,259	05/03/2016	9326966	HOR0026-201TC2-US	3046

101325 7590 04/13/2016

GLOBAL PATENT GROUP - HOR
1005 NORTH WARSON ROAD
SUITE 404
SAINT LOUIS, MO 63132

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):

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