

***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  $\mu\text{mol/L}$ .

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

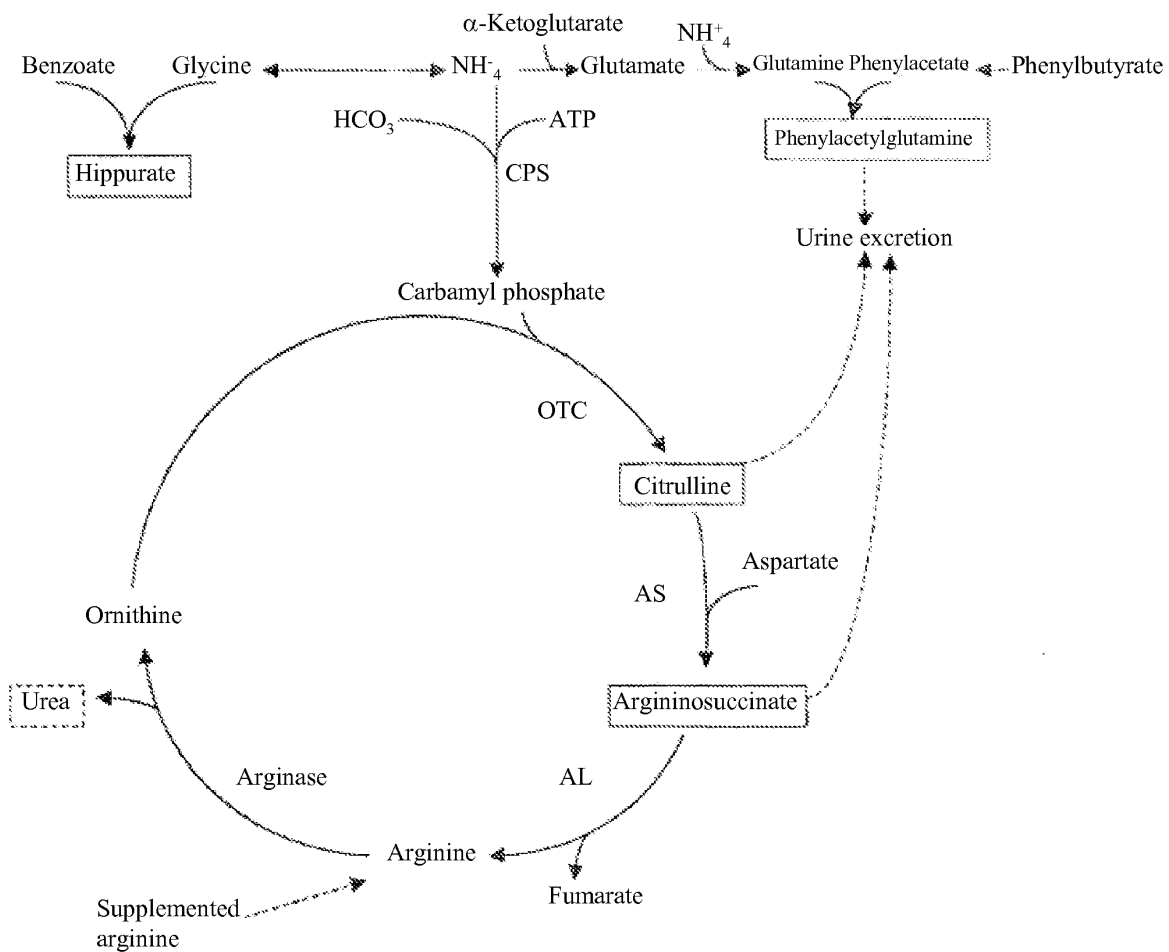


Figure 2

Relationship between Fasting Ammonia and AUC of Ammonia 0–24 hours  
Linear Regression and 95% ci of Prediction  
All Studies combined – 65 unique subjects

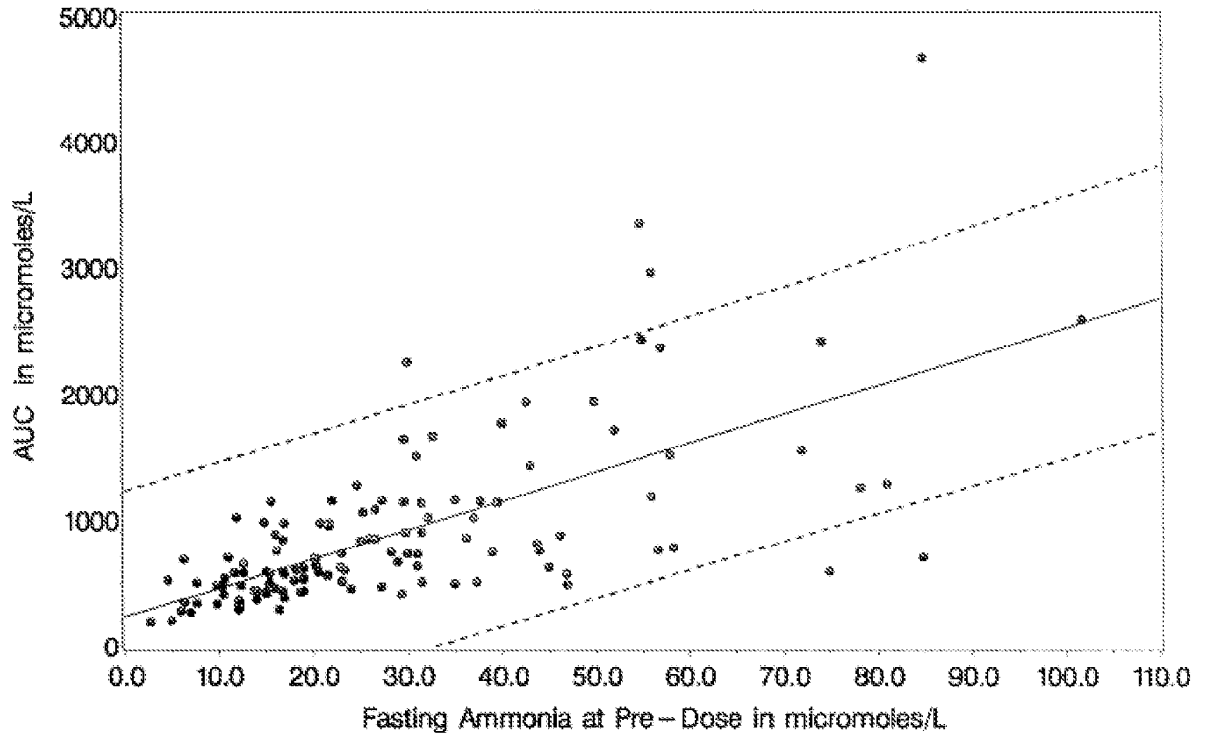
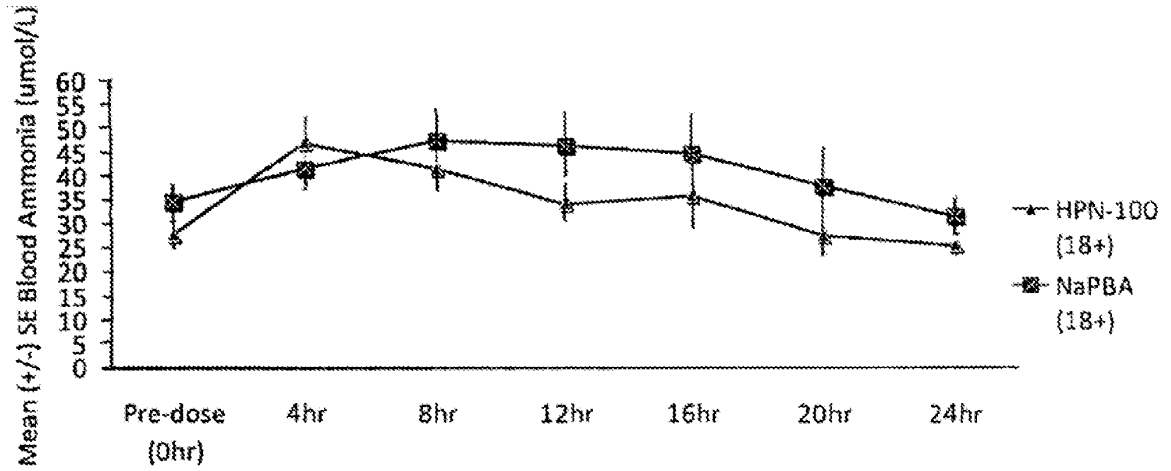
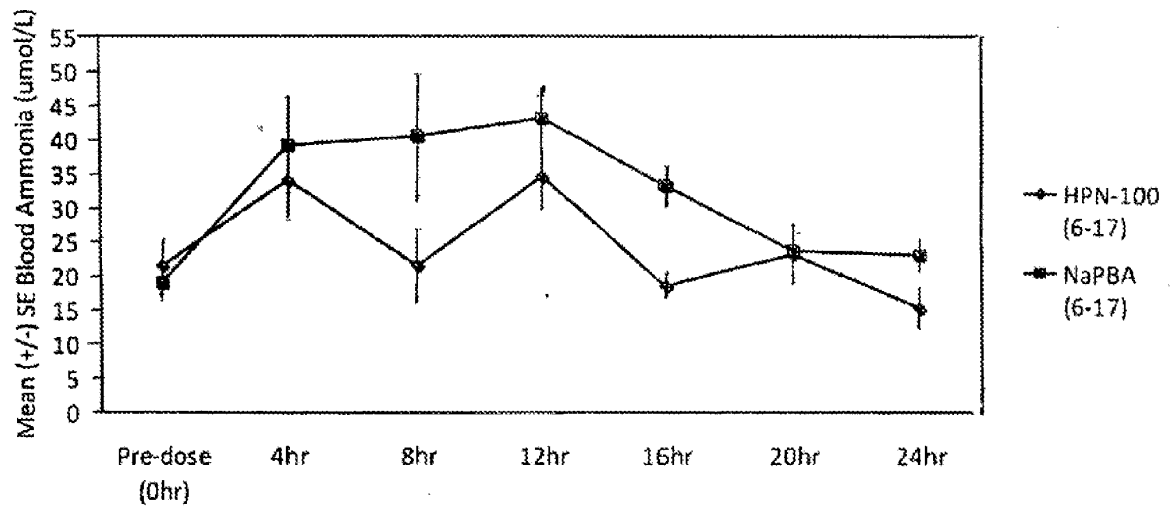


Figure 3

A.



B.





Attorney Docket No.: HOR0026-201TC2-US

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



**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 in 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)**

<b>Title of Invention</b>	<b>METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS</b>
---------------------------	---

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.

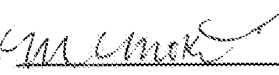
I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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



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

<b>Title of Invention</b>	<b>METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS</b>
---------------------------	---

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.

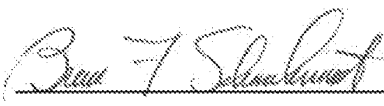
I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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

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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:**  **Date:** 3/15/13



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:

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 Date (Optional)
Name
Title

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 38 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

<b>Application Number:</b>				
<b>Filing Date:</b>				
<b>Title of Invention:</b>	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS			
<b>First Named Inventor/Applicant Name:</b>	Bruce Scharschmidt			
<b>Filer:</b>	Lauren Stevens/Vicki Truman			
<b>Attorney Docket Number:</b>	HOR0026-201TC2-US			
Filed as Large Entity				
<b>Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
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
<b>Pages:</b>				
<b>Claims:</b>				
Independent claims in excess of 3	1201	1	420	420
<b>Miscellaneous-Filing:</b>				

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
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
<b>Extension-of-Time:</b>				
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>6160</b>

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	24255987
<b>Application Number:</b>	14958259
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	3046
<b>Title of Invention:</b>	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
<b>First Named Inventor/Applicant Name:</b>	Bruce Scharschmidt
<b>Customer Number:</b>	101325
<b>Filer:</b>	Lauren Stevens/Vicki Truman
<b>Filer Authorized By:</b>	Lauren Stevens
<b>Attorney Docket Number:</b>	HOR0026-201TC2-US
<b>Receipt Date:</b>	03-DEC-2015
<b>Filing Date:</b>	
<b>Time Stamp:</b>	15:52:55
<b>Application Type:</b>	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 <small>dc7a23d1c02d00127f4e2eb322b611cac3e23ea1</small>	no	7

**Warnings:**

**Information:**

2		20150803_Application.pdf	402212 <small>359f789338e8b148193488d0084a2a451c1b3ca0</small>	yes	38
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**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 <small>53fd378a51373bca845c60df09ee47b7aadbabf6</small>	yes	7
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**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

<b>Warnings:</b>					
<b>Information:</b>					
4	Drawings-only black and white line drawings	20151203_Replacement_Drawings.pdf	232781 3758b55e524cbccad3058b4c0d977f854fd05fc	no	3
<b>Warnings:</b>					
<b>Information:</b>					
5	Transmittal Letter	20151203_IDS_Trans.pdf	19803 945e24ec6e8d5035af4c04725437098188eb936f	no	2
<b>Warnings:</b>					
<b>Information:</b>					
6	Information Disclosure Statement (IDS) Form (SB08)	20151203_IDS.pdf	291681 3dfcfa9988f10a6200dffee6382a80356a99109	no	21
<b>Warnings:</b>					
<b>Information:</b>					
This is not an USPTO supplied IDS fillable form					
7	Internet Communications Authorized	20151203_Internet_Communication_Authorization.pdf	74953 ce00537b44432f7ea3c89792086cef2d61fd52b7	no	2
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<b>Information:</b>					
8	Miscellaneous Incoming Letter	20151203_Notice_Related_Litigation.pdf	20958 b6e412ae057f4a8c307607653aa45df39906532c	no	2
<b>Warnings:</b>					
<b>Information:</b>					
9	Non Patent Literature	Xie_G_2012_Gastroenterology_142_918-927_124110051_1.PDF	6518066 3257c9a1c2831745b17a551bed9a2f6a2512081a	no	16
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10	Non Patent Literature	20151106_Lupin_Second_Notice_Letter_559.pdf	1629327 b4f5324a30ae330ba548ad311b6a3ecfc98cab751a	no	30
<b>Warnings:</b>					
<b>Information:</b>					
11	TrackOne Request	20151203_Track_1.pdf	113876 ddf3c5045897fc63eda016192a2f4da8abb69688	no	2
<b>Warnings:</b>					
<b>Information:</b>					

12	Oath or Declaration filed	20151203_Declaration.pdf	156713 c2a093eea2c007ed44bb62903448844bc1ff69705	no	2
<b>Warnings:</b>					
<b>Information:</b>					
13	Power of Attorney	Horizon_Therapeutics_Application.pdf	106357 674dfc6ed140e4b2710f2e8e0c1dae0af853ed0	no	1
<b>Warnings:</b>					
<b>Information:</b>					
14	Fee Worksheet (SB06)	fee-info.pdf	41998 6a94182274680dbe8778f90bcc69fae771ad9c1	no	2
<b>Warnings:</b>					
<b>Information:</b>					
<b>Total Files Size (in bytes):</b>				11467623	
<p>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.</p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  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.</p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  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.</p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  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.</p>					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	HOR0026-201TC2-US
		Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS		
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### Inventor Information:

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<b>Prefix</b>	<b>Given Name</b>	<b>Middle Name</b>	<b>Family Name</b>	<b>Suffix</b>	
	Bruce		Scharschmidt		
<b>Residence Information (Select One)</b> <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
<b>City</b>	San Francisco	<b>State/Province</b>	CA	<b>Country of Residence i</b>	US
<b>Mailing Address of Inventor:</b>					
<b>Address 1</b>	45 St. Francis Boulevard				
<b>Address 2</b>					
<b>City</b>	San Francisco	<b>State/Province</b>	CA		
<b>Postal Code</b>	94127	<b>Country i</b>	US		
<b>Inventor 2</b>					<input type="button" value="Remove"/>
<b>Legal Name</b>					
<b>Prefix</b>	<b>Given Name</b>	<b>Middle Name</b>	<b>Family Name</b>	<b>Suffix</b>	
	Masoud		Mokhtarani		
<b>Residence Information (Select One)</b> <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
<b>City</b>	Walnut Creek	<b>State/Province</b>	CA	<b>Country of Residence i</b>	US
<b>Mailing Address of Inventor:</b>					
<b>Address 1</b>	725 Castle Rock Road				
<b>Address 2</b>					
<b>City</b>	Walnut Creek	<b>State/Province</b>	CA		
<b>Postal Code</b>	94598	<b>Country i</b>	US		
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<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	HOR0026-201TC2-US
		Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS		

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**Application Information:**

Title of the Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS		
Attorney Docket Number	HOR0026-201TC2-US	<b>Small Entity Status Claimed</b> <input type="checkbox"/>	
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	3	<b>Suggested Figure for Publication (if any)</b>	

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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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<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	HOR0026-201TC2-US
		Application Number	
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Prior Application Status	Pending		<input type="button" value="Remove"/>		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)		
	Continuation of	14/816674	2015-08-03		
Prior Application Status	Patented		<input type="button" value="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		<input type="button" value="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		<input type="button" value="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		<input type="button" value="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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<b>Application Data Sheet 37 CFR 1.76</b>		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.
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<b>Application Data Sheet 37 CFR 1.76</b>	Attorney Docket Number	HOR0026-201TC2-US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

<b>Applicant 1</b>				<input type="button" value="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.				
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<input checked="" type="radio"/> Assignee	<input type="radio"/> Legal Representative under 35 U.S.C. 117	<input type="radio"/> Joint Inventor		
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Name of the Deceased or Legally Incapacitated Inventor : <input type="text"/>				
If the Applicant is an Organization check here. <input checked="" type="checkbox"/>				
Organization Name	Horizon Therapeutics, Inc.			
<b>Mailing Address Information For Applicant:</b>				
Address 1	520 Lake Cook Road			
Address 2	Suite 520			
City	Deerfield	State/Province	IL	
Country <sup>i</sup>	US	Postal Code	60015	
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<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	HOR0026-201TC2-US	
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Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS			

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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).

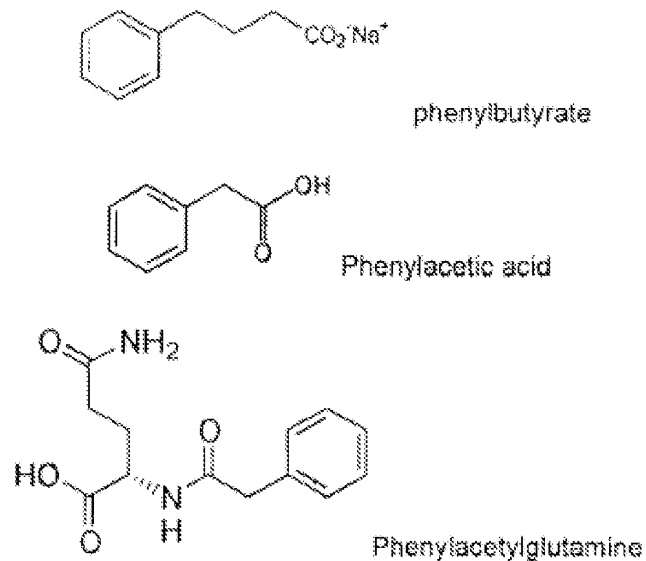
[0003] UCDs include several inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia, including enzymes involved in the urea cycle. The urea cycle is depicted in Figure 1, which also illustrates how certain ammonia-scavenging drugs act to assist in elimination 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 ( $\text{NH}_4^+$ ) 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<sup>®</sup> and in Europe as AMMONAPS<sup>®</sup>) 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.



**[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  $\mu\text{mol/L}$  or 59  $\mu\text{g/mL}$ . 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  $\mu\text{mol/L}$  or 59  $\mu\text{g/mL}$ . 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 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  $\mu\text{g/mL}$ . 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  $\leq -18^{\circ}\text{C}$  ( $\leq 0^{\circ}\text{F}$ ) 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  $\text{NH}^{4+}$  and NADPH to form glutamate and  $\text{NADP}^{+}$ . The formation of  $\text{NADP}^{+}$  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  $\mu\text{mol/L}$ . 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 reagents, 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.,  $\mu\text{g/mL}$  or  $\mu\text{mol/L}$ ), 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  $\mu\text{mol/L}$ . In certain of these embodiments, the ULN for blood ammonia may be in the range of 32-38  $\mu\text{mol/L}$  or 34-36  $\mu\text{mol/L}$ , and in certain of these embodiments the ULN for blood ammonia is 35  $\mu\text{mol/L}$ . In certain embodiments, the ULN for blood ammonia may be in the range of 50-65  $\mu\text{g/mL}$ . In certain of these embodiments, the ULN for blood ammonia may be in the range of 55-63  $\mu\text{g/mL}$  or 57-61  $\mu\text{g/mL}$ , and in certain of these embodiments the ULN for blood ammonia is 59  $\mu\text{g/mL}$ .

**[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  $\text{AUC}_{0-24\text{hr}}$ ) obtained from adequate and well-spaced samples over 24 hours. This ammonia  $\text{AUC}_{0-24\text{hr}}$  can be further normalized for the entire actual period of sampling, i.e., ammonia  $\text{AUC}_{0-24\text{hr}}$  is divided by the sampling period (e.g., 24 hours). For example, if an AUC of 1440  $\mu\text{mol}\cdot\text{hr/L}$  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  $\text{AUC}_{0-24\text{hr}}$  would be equal to 1440  $\mu\text{mol}\cdot\text{hr/ml}$  divided by the sampling time of 24 hr, or 60  $\mu\text{mol/L}$ . If the normal reference range at the laboratory which performed the ammonia analysis was 10-35  $\mu\text{mol/L}$ , then the average daily ammonia value for this subject would be approximately 1.71 times the ULN of 35  $\mu\text{mol/L}$ . Similarly, if the ammonia  $\text{AUC}_{0-24\text{hr}}$  was determined to be equal to 840  $\mu\text{mol}\cdot\text{hr/L}$  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  $\text{AUC}_{0-24\text{hr}}$  would be 35  $\mu\text{mol/L}$ . 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  $\mu\text{mol/L}$  and clinical manifestations of hyperammonemia, which may require intervention to prevent irreversible harm 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 ( $C_{\text{max}}$ ) over 24 hours that exceeds 100  $\mu\text{mol/L}$ . It has been found that 100  $\mu\text{mol/L}$  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  $\mu\text{mol/L}$ ) 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  $\mu\text{mol/L}$ ); and an average likelihood of 25% that his or her maximal daily ammonia level exceeds 100  $\mu\text{mol/L}$  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  $\pm$ 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  $\mu\text{mol/L}$ . 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:

<b>Gender n (%)</b>	Male	18 (27.7)
	Female	47 (72.3)
<b>Age at screening (years)</b>	N	65
	Mean (SD)	29.46 (15.764)
	Median	24.00
	Range	6.0-75.0
<b>UCD diagnosis n (%)</b>	OTC deficiency	57 (87.7)
	CPS1 deficiency	1 (1.5)
	ASS deficiency	5 (7.7)
	ASL deficiency	1 (1.5)
	Missing	1 (1.5)
<b>Duration of NaPBA treatment (months)</b>	N	63
	Mean (SD)	114.14 (90.147)
	Median	101.00
	Range	0.2-300.0
<b>Daily dose NaPBA</b>	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:  $\text{AUC}_{0-24\text{hr}}$ , time-normalized AUC, log AUC, maximal ammonia value over 24 hours ( $C_{\text{max}}$ ), 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  $AUC_{0-24hr}$  and (2) fasting ammonia and maximum observed ammonia ( $C_{max}$ ) 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  $AUC_{0-24hr}$ , with increasing fasting ammonia being associated with higher  $AUC_{0-24hr}$  and maximum observed ammonia (Figure 2).

[0070] Prediction of  $AUC_{0-24hr}$  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  $\mu\text{mol/L}$ , 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)  $C_{max}$  [0-1.0\*ULN, >1.0\*ULN];
- 4)  $C_{max}$  [0-1.5\*ULN, >1.5\*ULN]; and
- 5)  $C_{max}$  [0-100]  $\mu\text{mol/L}$ .

[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<sub>0-24hr</sub> in the normal range [AUC<sub>0-24hr</sub> 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 1.5 ULN, and a 93% chance (with a 95% confidence

interval of 78% to 100%) of never having an ammonia of more than 100  $\mu\text{mol/L}$ . 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  $\text{AUC}_{0-24\text{hr}}$  in the normal range (0-840 or an average daily ammonia of 35  $\mu\text{mol/L}$ ).

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  $\mu\text{mol/L}$ . This fasting blood ammonia level is compared to the ULN for blood ammonia in the laboratory performing the blood draw, which is 35  $\mu\text{mol/L}$ . 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  $\text{m}^2$ , 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-100 for at least 7 days, and returns for an additional blood draw. The fasting blood ammonia level at this time is 33  $\mu\text{mol/L}$ , 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-100 with each meal. It is observed that Patient A's maximum ammonia reaches 95  $\mu\text{mol/L}$  after

dinner with an average daily ammonia of 66  $\mu\text{mol/L}$ , 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  $\mu\text{mol/L}$ , 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  $\mu\text{mol/L}$ , 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  $\mu\text{mol/L}$  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<sup>®</sup> per day, amino acid supplements, and restricted dietary protein intake. Patient B does not consume BUPHENYL<sup>®</sup>, 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  $\mu\text{mol/L}$ . This fasting blood ammonia level is compared to the ULN for blood ammonia for the laboratory performing the blood draw, which is 35  $\mu\text{mol/L}$ . 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  $\mu\text{mol/L}$  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<sup>®</sup> Patient B was receiving, and it is determined that Patient B needs to take 10.5 mL of HPN-100 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  $\mu\text{mol/L}$ , 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  $\mu\text{mol/L}$ , 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  $\mu\text{mol/L}$  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  $\mu\text{mol/L}$ . This fasting blood ammonia level is compared to the ULN for blood ammonia for the laboratory performing the blood draw, which is 35  $\mu\text{mol/L}$ . 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  $\mu\text{mol/L}$  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  $\mu\text{mol/L}$ , 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  $\mu\text{mol/L}$ , 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  $\mu\text{mol/L}$ , 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  $\mu\text{mol/L}$  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  $\mu\text{mol/L}$  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  $\mu\text{mol/L}$  before enrollment to 166  $\mu\text{mol/L}$  during the study. Fasting ammonia remained controlled and monthly averages were at or close to half ULN, ranging from 17 to 22  $\mu\text{mol/L}$ . 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., C<sub>max</sub>) 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 m<sup>2</sup>, 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/m<sup>2</sup> of NaPBA was ~13%-22% lower in adults than NaPBA (C<sub>max</sub> = 82 vs. 106 µg/mL; AUC<sub>0-24</sub> = 649 vs. 829 µg.h/m) and ~13% higher in pediatric subjects ages 6-17 than NaPBA (C<sub>max</sub> = 154 vs. 138 µg/mL; AUC<sub>0-24</sub> = 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<sup>2</sup> 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  $\mu\text{mol/L}$ .
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

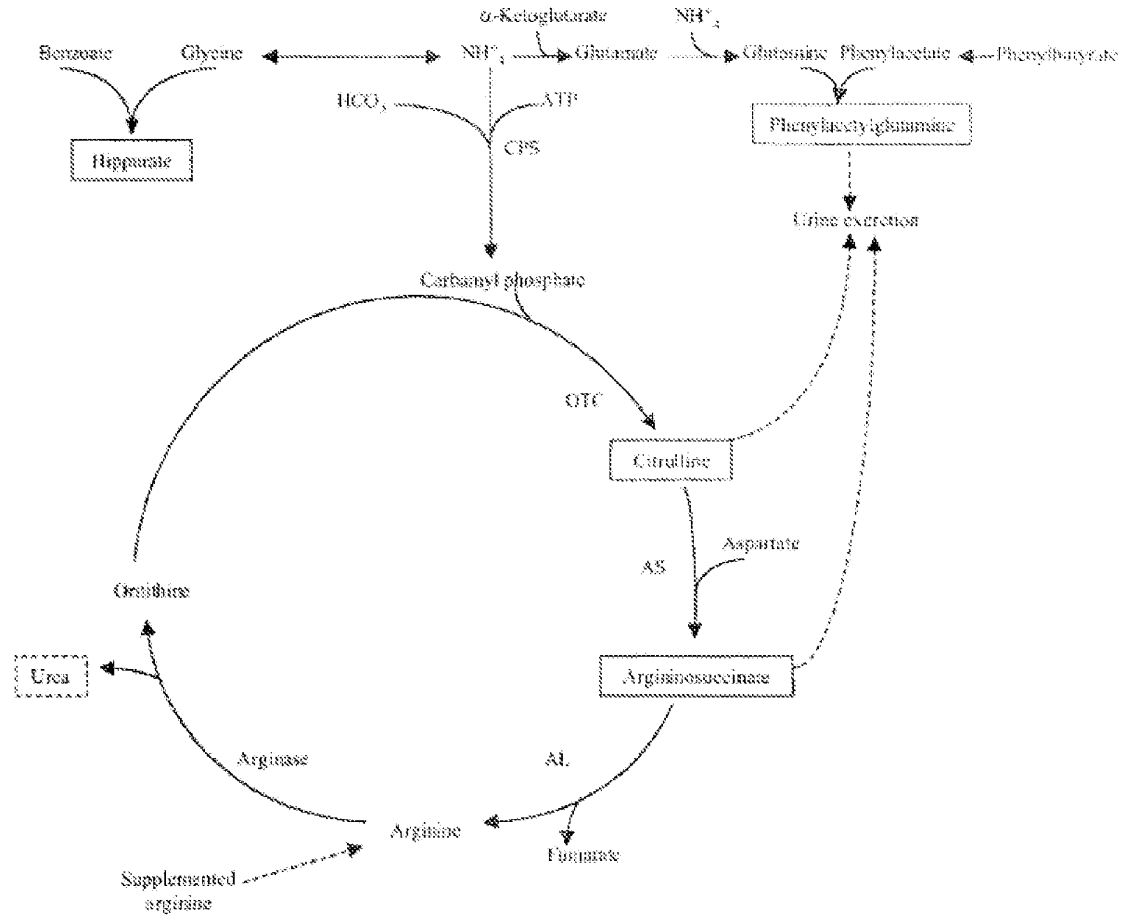
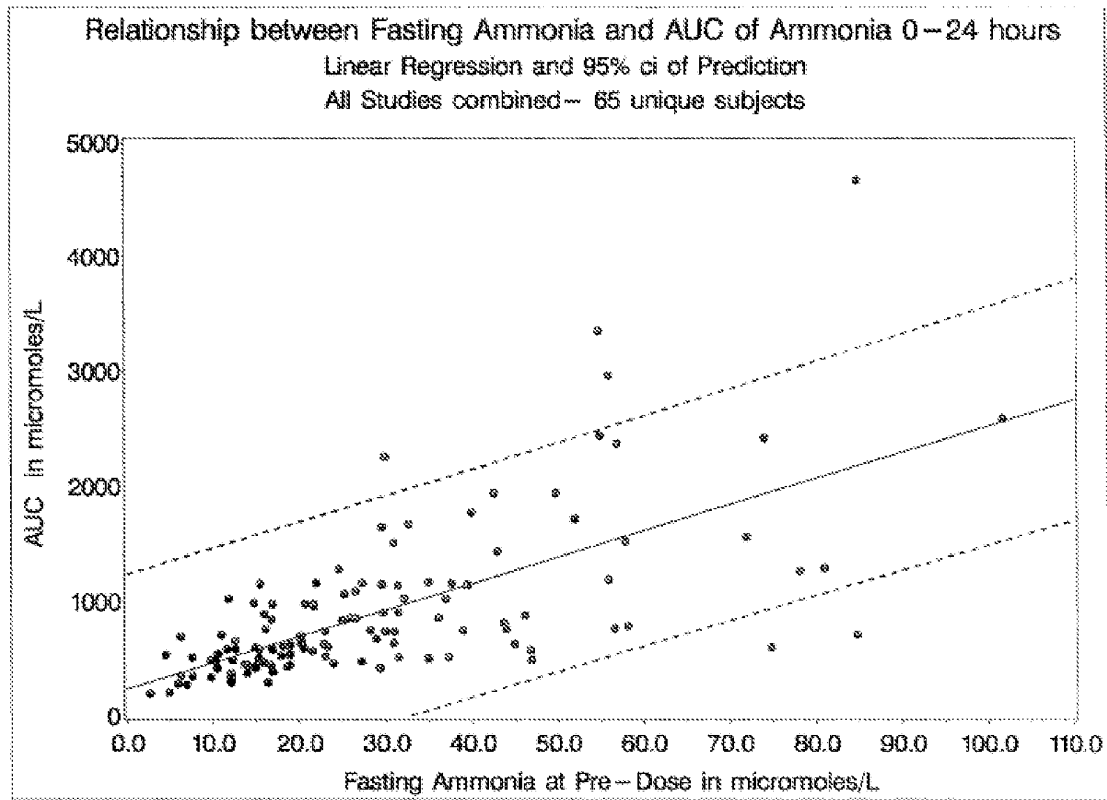
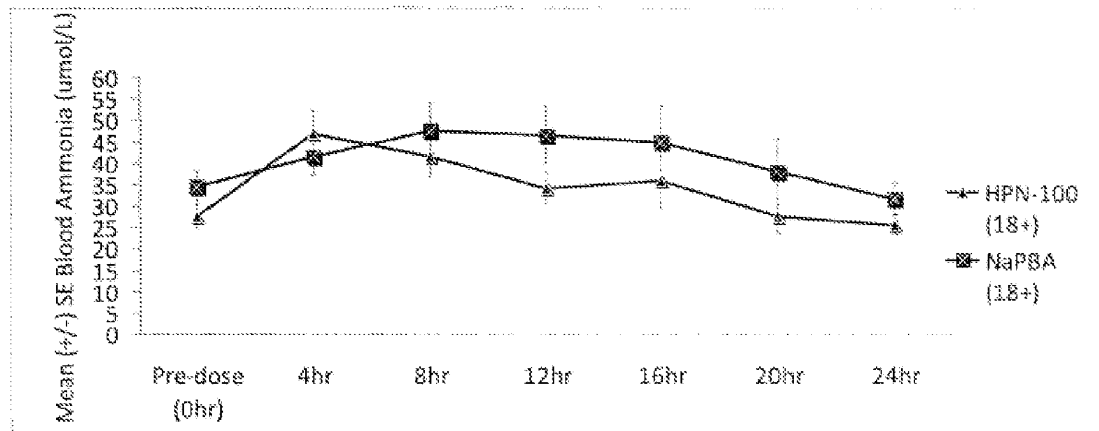


Figure 2

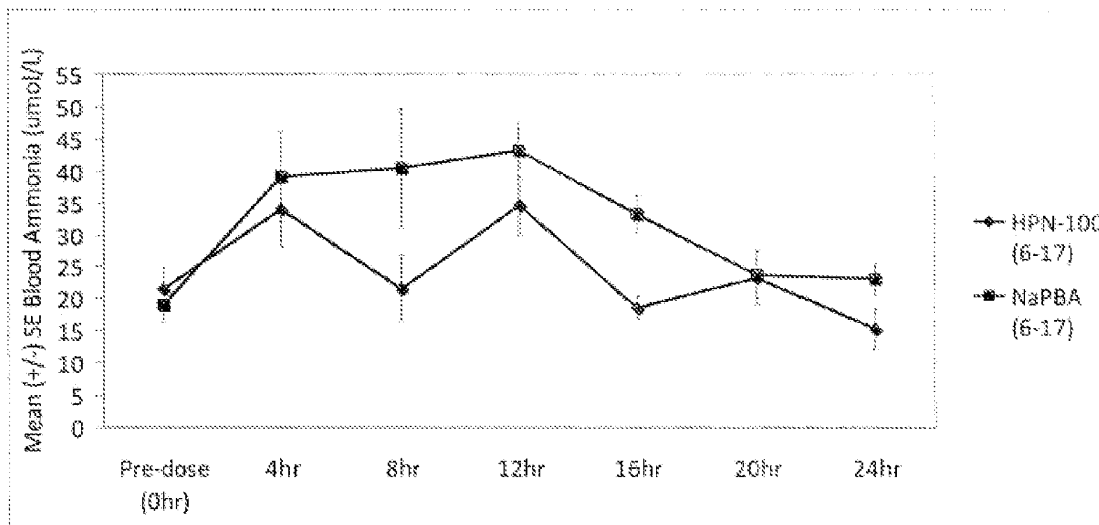


**Figure 3**

**A.**



**B.**





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		Number-Kind Code <sup>2</sup> (if known)			
	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	
	P7	6,219,567	04-17-2001	Cardiox Corporation	
	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	
	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	
	P16	2008/0119554	05-22-2008	Rajiv Jalan et al	
	P17	2010/0008859	01-14-2010	Hyperion Therapeutics, Inc.	
	P18	2010/0016207	01-21-2010	Wurtman, RJ et al	
	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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	D4	ANDA Notice Letter, Par Pharmaceutical, Inc. to Hyperion Therapeutics, inc.. Re: Glycerol Phenylbutyrate 1.1 gm/ml oral liquid; United States Patent Nos. 8,404,215 and 8,642,012 Notice of Paragraph IV Certification March 12, 2014.	

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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	
	D6	ANDA Notice Letter, Lupin Ltd. to Horizon Therapeutics, Inc.. Re: Notification of Invalidity, Unenforceability, and/or Noninfringement for U.S. Patent No. 9,095,559 Pursuant to § 505(j)(2)(B)(ii) and (iv) of the Federal Food, Drug, and Cosmetic Act, Nov. 6, 2015	
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	D9	BATSHAW, M.L. et al., "Treatment of Inborn Errors of Urea Synthesis: Activation of Alternative Pathways of Waste Nitrogen Synthesis and Excretion", 306 N. Engl. J. Med. 1387 (1982).	
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	D70	Examination Report mailed May 11, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on Aug. 27, 2009, one page.	
	D71	Examination Report mailed on Oct. 27, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on Aug. 27, 2009, two pages.	
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<i>(use as many sheets as necessary)</i>				<b>Filing Date</b>	TBD
Sheet 18 of 21				<b>First Named Inventor</b>	Bruce Scharschmidt
				<b>Art Unit</b>	TBD
				<b>Examiner Name</b>	TBD
				<b>Attorney Docket Number</b>	HOR0026-201TC2-US

NON PATENT LITERATURE DOCUMENTS			
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	D183	SHERWIN, C. et al., "The Maximum Production of Glutamine by the Human Body as Measured by the Output of Phenylacetylglutamine", 37 J. Biol. Chem. 113 (1919).	
	D184	SHIPLE, G.J. et al., "Synthesis of Amino Acids in Animal Organisms. I. Synthesis of Glycocoll and Glutamine in the Human Organism", 44 J. Am. Chem. Soc. 618 (1922).	
	D185	SIMELL, O., et al., "Waste Nitrogen Excretion Via Amino Acid Acylation: Benzoate and Phenylacetate in Lysinuric Protein Intolerance", 20 Pediatr. Res. 1117 (1986).	
	D186	SINGH, "Consensus Statement from a Conference for the Management of Patients with Urea Cycle Disorders", 138 J. Pediatrics S1 (2001).	
	D187	SMITH, W., et al., "Ammonia Control in Children Ages 2 Months through 5 Years with Urea Cycle Disorders: Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate," J Pediatr. 162(6):1228-1234.e1 (2013).	
	D188	STAUCH, et al., (1998) "Oral L-ornithine-L-aspartate therapy of chronic hepatic encephalopathy: results of a placebo-controlled double-blind study" J Hepatology 28(5):856-864.	
	D189	SUMMAR, M., "Current Strategies for the Management of Neonatal Urea Cycle Disorders", 138 J. Pediatrics S30 (2001).	
	D190	SUMMAR, M. and Tuchman, M., "Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders", 138 J. Pediatrics S6 (2001).	
	D191	SUMMAR, M., "Urea Cycle Disorders Overview, Gene Reviews", www.genetests.org (Apr. 2003).	
	D192	SUMMAR, M. et al., "Unmasked Adult-Onset Urea Cycle Disorders in the Critical Care Setting", 21 Crit. Care Clin. S1 (2005).	
	D193	SUMMAR, M. et al., "Description and Outcomes of 316 Urea Cycle Patients From a 21- Year, Multicenter Study of Acute Hyperammonemic Episodes", Abstract, presented at Annual Symposium CCH-Congress Centre Hamburg, Sep. 4-7, 2007, GSSIEM 2007, two pages.	
	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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				<b>Filing Date</b>	TBD
<i>(use as many sheets as necessary)</i>				<b>First Named Inventor</b>	Bruce Scharschmidt
				<b>Art Unit</b>	TBD
Sheet 19 of 21				<b>Examiner Name</b>	TBD
				<b>Attorney Docket Number</b>	HOR0026-201TC2-US

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Examiner Initials*	Cite No. <sup>1</sup>	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 <sup>6</sup>
	D195	Swedish Orphan International, "Urea Cycle Disorders an International Perspective", Poster, Symposium Swedish Orphan International, Barcelona, Spain, Jan. 12, 2007, one page.	
	D196	TANNER, L. M., et al., "Nutrient Intake in Lysinuric Protein Intolerance", 30 J. Inherit. Metab. Dis. 716 (2007).	
	D197	The National Organization for Rare Disorders (2012). The Physician's Guide to Urea Cycle Disorders, at <a href="http://nordphysicianguides.org/wp-content/uploads/2012/02/NORD_Physician_Guide_to_Urea_Cycle_Disorders.pdf">http://nordphysicianguides.org/wp-content/uploads/2012/02/NORD_Physician_Guide_to_Urea_Cycle_Disorders.pdf</a>	
	D198	THIBAUT, A., et al., "A Phase I and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer", 54 Cancer Res. 1690 (1994).	
	D199	THIBAUT, A., et al., "Phase I Study of Phenylacetate Administered Twice Daily to Patients with Cancer", 75 Cancer 2932 (1995).	
	D200	TODO, S. et al., "Orthotopic Liver Transplantation for Urea Cycle Enzyme Deficiency", 15 Hepatology 419 (1992).	
	D201	TUCHMAN, M., and Yudkoff, M., "Blood Levels of Ammonia and Nitrogen Scavenging Amino Acids in Patients with Inherited Hyperammonemia", 66 Molecular Genetics and Metabolism 10-15 (1999).	
	D202	TUCHMAN, M. et al., Cross-Sectional Multicenter Study of Patients With Urea Cycle Disorders in the United States, 94 Molec. Genetics Metab. 397 (2008, e-pub. Jun. 17, 2008).	
	D203	UMass Memorial Medical Center, Lab Updates, "Measurement of Ammonia in Blood." February 2007. Accessed at <a href="http://www.ummlabs.org/News/07Feb.pdf">www.ummlabs.org/News/07Feb.pdf</a> .	
	D204	United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2009/030362, mailed March 2, 2009.	
	D205	United States Patent and Trademark Office, International Search Report and Written Opinion dated Jun. 4, 2012 for PCT/US2012/028620.	
	D206	United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2012/54673 mailed November 20, 2012.	

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Sheet 20 of 21				<b>Examiner Name</b>	TBD
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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.	
	D210	VILSTRUP, H., et al., "Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver," Hepatology 60 (2):715-735 (2014).	
	D211	WALSH et al., Chemical Abstract vol. 112, No. 231744	
	D212	WALSH et al., THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 8, pp. 4374-4381 (1990), "sn-1,2-Diacylglycerol Kinase of Escherichia coli".	
	D213	WATERLOW, J.C., The Partition of Nitrogen in the Urine of Malnourished Jamaican Infants, 12 Am. J. of Clin. Nutrition 235 (1963).	
	D214	WELBOURNE, T. et al., "The Effect of Glutamine Administration on Urinary Ammonium Excretion in Normal Subjects and Patients with Renal Disease", 51 J. Clin. Investigation 1852 (1972).	
	D215	WICKEN, B., "Problems in the Management of Urea Cycle Disorders", 81 Molecular Genetics and Metabolism 85 (2004).	
	D216	WILSON, C.J., et al., "Plasma Glutamine and Ammonia Concentrations in Ornithine Carbamoyltransferase Deficiency and Citrullinaemia", 24 J. Inherited Metabolic Disease 691 (2001).	
	D217	WRIGHT, G., et al., "Management of Hepatic Encephalopathy", 2011 International Journal of Hepatology 1 (2011).	
	D218	WRIGHT, P., Review: "Nitrogen Excretion: Three End Products, Many Physiological Roles", 198 J. Experimental Biology 273 (1995).	

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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	
	D220	YAJIMA, et al. "Diurnal Fluctuations of Blood Ammonia Levels in Adult-Type Citrullinemia", 137 Tokohu J. Ex/ Med, 213-220 (1982)	
	D221	YU, Ryan and Potter, Murray, "Diagnosis of Urea Cycle Disorders in Adulthood: Late- Onset Carbamyl Phosphate Synthetase 1 Deficiency", 7 MUMJ 30 (2010).	
	D222	YUDKOFF, M. et al., "In Vivo Nitrogen Metabolism in Ornithine Transcarbamylase Deficiency", 98 J. Clin. Invest. 2167 (1996).	
	D223	ZEITLIN, P., "Novel Pharmacologic Therapies for Cystic Fibrosis", 103 J. Clinical Investigation 447 (1999).	
	D224	ZEITLIN, P.L. et al., "Evidence of CFTR Function in Cystic Fibrosis After System Administration of 4-Phenylbutyrate", 6 Mol. Therapy 119 (2002).	

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

**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



Atty Docket No.: HOR0026-201TC2-US

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<sup>®</sup> (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

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<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875	Application or Docket Number <b>14/958,259</b>	Filing Date <b>12/03/2015</b>	<input type="checkbox"/> To be Mailed
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ENTITY:    LARGE    SMALL    MICRO

**APPLICATION AS FILED – PART I**

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	
<input type="checkbox"/> 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 \$ =	
<input type="checkbox"/> 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).			
<input type="checkbox"/> 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**

	(Column 1)	(Column 2)	(Column 3)	(Column 4)	RATE (\$)	ADDITIONAL FEE (\$)
<b>AMENDMENT</b>	<b>12/03/2015</b>	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	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
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					
					TOTAL ADD'L FEE	<b>0</b>

	(Column 1)	(Column 2)	(Column 3)	(Column 4)	RATE (\$)	ADDITIONAL FEE (\$)
<b>AMENDMENT</b>		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
	<input type="checkbox"/> 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**

		(Column 1)	(Column 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR		NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	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), (j), 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		OR	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)	(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=		OR	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=		OR	x	=
Application Size Fee (37 CFR 1.16(s))							OR		
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=		OR	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=		OR	x	=
Application Size Fee (37 CFR 1.16(s))							OR		
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  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
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



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
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

Table with 7 columns: APPLICATION NUMBER, FILING or 371(c) DATE, GRP ART UNIT, FIL FEE REC'D, ATTY. DOCKET NO, TOT CLAIMS, IND CLAIMS. Row 1: 14/958,259, 12/03/2015, 1629, 2020, HOR0026-201TC2-US, 10, 4

CONFIRMATION NO. 3046

FILING RECEIPT



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

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).

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**Title 35, United States Code, Section 184**  
**Title 37, Code of Federal Regulations, 5.11 & 5.15**

**GRANTED**

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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 Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

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***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  $\mu\text{mol/L}$ .

23. (New) The method of claim 22, wherein the upper limit of normal for plasma ammonia level is in the range of 32-38  $\mu\text{mol/L}$ .

24. (New) The method of claim 23, wherein the upper limit of normal for plasma ammonia level is in the range of 34-36  $\mu\text{mol/L}$ .

25. (New) The method of claim 22, wherein the upper limit of normal for plasma ammonia level is in the range of 55-63  $\mu\text{g/mL}$ .
26. (New) The method of claim 25, wherein the upper limit of normal for plasma ammonia level is in the range of 57- 61  $\mu\text{g/mL}$ .
27. (New) The method of claim 26, wherein the upper limit of normal for plasma ammonia level is 59  $\mu\text{g/mL}$ .
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  $\mu\text{g/L}$ .

31. (New) The method of claim 30, wherein the upper limit of normal for plasma ammonia level is in the range of 55-63  $\mu\text{g/mL}$ .
32. (New) The method of claim 31, wherein the upper limit of normal for plasma ammonia level is in the range of 57-61  $\mu\text{g/mL}$ .
33. (New) The method of claim 32, wherein the upper limit of normal for plasma ammonia level is 59  $\mu\text{g/mL}$ .
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

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

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

Electronic Patent Application Fee Transmittal				
<b>Application Number:</b>	14958259			
<b>Filing Date:</b>	03-Dec-2015			
<b>Title of Invention:</b>	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS			
<b>First Named Inventor/Applicant Name:</b>	Bruce Scharschmidt			
<b>Filer:</b>	Brock D. Levin/Vicki Truman			
<b>Attorney Docket Number:</b>	HOR0026-201TC2-US			
Filed as Large Entity				
<b>Filing Fees for Utility under 35 USC 111(a)</b>				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Basic Filing:</b>				
<b>Pages:</b>				
<b>Claims:</b>				
Independent claims in excess of 3	1201	1	420	420
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Extension-of-Time:</b>				
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>420</b>

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	24634825
<b>Application Number:</b>	14958259
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	3046
<b>Title of Invention:</b>	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
<b>First Named Inventor/Applicant Name:</b>	Bruce Scharschmidt
<b>Customer Number:</b>	101325
<b>Filer:</b>	Brock D. Levin/Vicki Truman
<b>Filer Authorized By:</b>	Brock D. Levin
<b>Attorney Docket Number:</b>	HOR0026-201TC2-US
<b>Receipt Date:</b>	15-JAN-2016
<b>Filing Date:</b>	03-DEC-2015
<b>Time Stamp:</b>	14:14:02
<b>Application Type:</b>	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 4ed77ea68a4f68df096230740efd3ae63fdfa440	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
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**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.

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.

<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875	Application or Docket Number <b>14/958,259</b>	Filing Date <b>12/03/2015</b>	<input type="checkbox"/> To be Mailed
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ENTITY:  LARGE  SMALL  MICRO

**APPLICATION AS FILED – PART I**

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (j), or (m))	N/A	N/A	N/A	
<input type="checkbox"/> 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 \$ =	
<input type="checkbox"/> 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).			
<input type="checkbox"/> 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**

	(Column 1)	(Column 2)	(Column 3)	(Column 4)	(Column 5)	RATE (\$)	ADDITIONAL FEE (\$)
<b>AMENDMENT</b>	<b>01/15/2016</b>	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA			
	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
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))						
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	<b>0</b>	

	(Column 1)	(Column 2)	(Column 3)	(Column 4)	(Column 5)	RATE (\$)	ADDITIONAL FEE (\$)
<b>AMENDMENT</b>		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA			
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))						
	<input type="checkbox"/> 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".  
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LIE  
/ANDREA FREEMAN/

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<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875	Application or Docket Number <b>14/958,259</b>	Filing Date <b>12/03/2015</b>	<input type="checkbox"/> To be Mailed
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ENTITY:  LARGE  SMALL  MICRO

**APPLICATION AS FILED – PART I**

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (j), or (m))	N/A	N/A	N/A	
<input type="checkbox"/> 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 \$ =	
<input type="checkbox"/> 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).			
<input type="checkbox"/> 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**

	(Column 1)	(Column 2)	(Column 3)	(Column 4)	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT	<b>01/15/2016</b>	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	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
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					
			TOTAL ADD'L FEE		<b>0</b>	

	(Column 1)	(Column 2)	(Column 3)	(Column 4)	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
	<input type="checkbox"/> 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.  
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LIE  
/LASHAWN MARKS/

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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

Table with 1 column: EXAMINER

RAO, SAVITHA M

Table with 2 columns: ART UNIT, PAPER NUMBER

1621

Table with 2 columns: NOTIFICATION DATE, DELIVERY MODE

01/29/2016

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vtruman@globalpatentgroup.com
LStevens@horizonpharma.com



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Doc Code:  
TRACK1.GRANT

<b>Decision Granting Request for Prioritized Examination (Track I or After RCE)</b>	Application No.: 14/958,259
<p>1. THE REQUEST FILED <u>12/3/15</u> IS <b>GRANTED</b>.</p> <p>The above-identified application has met the requirements for prioritized examination</p> <p>A. <input checked="" type="checkbox"/> for an original nonprovisional application (Track I).</p> <p>B. <input type="checkbox"/> for an application undergoing continued examination (RCE).</p> <p>2. <b>The above-identified application will undergo prioritized examination.</b> The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:</p> <p>A. filing a <b><u>petition for extension of time</u></b> to extend the time period for filing a reply;</p> <p>B. filing an <b><u>amendment to amend the application to contain more than four independent claims, more than thirty total claims</u></b>, or a multiple dependent claim;</p> <p>C. filing a <b><u>request for continued examination</u></b>;</p> <p>D. filing a notice of appeal;</p> <p>E. filing a request for suspension of action;</p> <p>F. mailing of a notice of allowance;</p> <p>G. mailing of a final Office action;</p> <p>H. completion of examination as defined in 37 CFR 41.102; or</p> <p>I. abandonment of the application.</p> <p>Telephone inquiries with regard to this decision should be directed to Terri Johnson at 571-272-2991</p> <p>/Terri Johnson/ <span style="float: right;">Paralegal Specialist</span></p> <p>_____</p> <p>[Signature] <span style="float: right;">(Title)</span></p>	

## 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.**

**GRANTED**

**DISMISSED**

**DENIED**

Office of Petitions: Decision Count Sheet

Mailing Month

1

Application No.

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



Decision Type: 643 - Track One request



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)

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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





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 claims 1-15 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 facie 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) comparing 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 facie 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 facie 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 1 of '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 mass 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 facie 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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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

Caplus now includes complete International Patent Classification (IPC) reclassification data for the fourth quarter of 2012.

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This file contains CAS Registry Numbers for easy and accurate 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")
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```
=> 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

$\mu\text{mol/L}$ ;  $C_{\text{max}} = 56.3$  vs.  $79.1 \mu\text{mol/L}$ ; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time-normalized AUC) by post hoc anal. Systemic exposure (AUC<sub>0-24</sub>) to PBA on GPB was 27% lower than on NaPBA ( $540$  vs.  $739 \mu\text{g h/mL}$ ), whereas exposure to phenylacetic acid (PAA) ( $575$  vs.  $596 \mu\text{g h/mL}$ ) and phenylacetylglutamine (PAGN) ( $1098$  vs.  $1133 \mu\text{g h/mL}$ ) 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

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 ENTRY SESSION  
 FULL ESTIMATED COST 11.77 13.45

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(FILE 'HOME' ENTERED AT 07:15:37 ON 16 NOV 2012)

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)  
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 USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: September 2012

Caplus now includes complete International Patent Classification (IPC) reclassification data for the fourth quarter of 2012.

CAS Information Use Policies apply and are available at:

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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 16 and scavenging
    44689 SCAVENGING
    20 SCAVENGINGS
    44704 SCAVENGING
      (SCAVENGING OR SCAVENGINGS)
L7   1850 L6 AND SCAVENGING

```

```

=> s 17 and PAA
    10799 PAA
    573 PAAS
    11191 PAA
      (PAA OR PAAS)
L8   1 L7 AND PAA

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=> d 18 ibib ab

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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  $\mu\text{mol/L}$ ;  $C_{\text{max}}$  = 56.3 vs. 79.1  $\mu\text{mol/L}$ ; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time-normalized AUC) by post hoc anal. Systemic exposure (AUC<sub>0-24</sub>) to PBA on GPB was 27% lower than on NaPBA (540 vs. 739  $\mu\text{g h/mL}$ ), whereas exposure to phenylacetic acid (PAA) (575 vs. 596  $\mu\text{g h/mL}$ ) and phenylacetylglutamine (PAGN) (1098 vs. 1133  $\mu\text{g h/mL}$ ) 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

=> 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)



=> 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 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN

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: CTMCL; 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  $\alpha, \beta$ -poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA),  $\alpha, \beta$ -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  $\alpha,\beta$ -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  $\alpha,\beta$ -poly (L-aspartic acid)-CPT conjugates were synthesized, and used to fabricate nanomicelle. Firstly,  $\alpha,\beta$ -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 spectrophotometry 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 Biomoléculaire, 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  $\mu$ M, while IC50 for BCH-189 in this system was 0.1  $\mu$ M. 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 RECORD (14 CITINGS)

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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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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")
    957090 "NITROGEN"
      4893 "NITROGENS"
    960515 "NITROGEN"
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    45123 "SCAVENGING"
      21 "SCAVENGINGS"
    45139 "SCAVENGING"
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("SCAVENGING" OR "SCAVENGINGS")  
33 "NITROGEN SCAVENGING"  
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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

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  $\mu\text{mol/L}$  (reference interval: 16-47  $\mu\text{mol/L}$ ) 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  $\mu\text{mol/L}$ ) or four times (188  $\mu\text{mol/L}$ ) 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): Ucyclid 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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ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
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,  
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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 acidemia  
AUTHOR(S): Scholl-Buerger, 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; Sperandio, 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  $\gamma$ -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

REFERENCE COUNT: 55 (8 CITINGS)  
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  $\mu\text{mol/L}$ ;  $C_{\text{max}}$  = 56.3 vs. 79.1  $\mu\text{mol/L}$ ; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time-normalized AUC) by post hoc anal. Systemic exposure (AUC<sub>0-24</sub>) to PBA on GPB was 27% lower than on NaPBA (540 vs. 739  $\mu\text{g h/mL}$ ), whereas exposure to phenylacetic acid (PAA) (575 vs. 596  $\mu\text{g h/mL}$ ) and phenylacetylglutamine (PAGN) (1098 vs. 1133  $\mu\text{g h/mL}$ ) 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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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, 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			
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
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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  $\mu\text{mol/dL}$ , and 3 patients had a maximal glutamine level of higher than 200  $\mu\text{mol/dL}$ . 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  $\mu\text{mol/L}$ . 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 ( $R^2 = 0.25$  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 NH<sub>4</sub><sup>+</sup>, SO<sub>4</sub><sup>2-</sup>, NO<sub>3</sub><sup>-</sup>, and Cl<sup>-</sup>, as well as airborne concns. of these species and gaseous HNO<sub>3</sub>, HCl, and NH<sub>3</sub>, 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 HNO<sub>3</sub> have only a rather minor influence upon wet deposition at this site. Gaseous NH<sub>3</sub> influences ground-level air chemical appreciably, but scavenging ratios for NH<sub>4</sub><sup>+</sup> are low, even when based upon aerosol NH<sub>4</sub><sup>+</sup> 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 NH<sub>3</sub> and N<sub>2</sub>O. 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 15N<sub>2</sub> was incorporated when bacteria were grown on 15N<sub>2</sub>, 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)

=> d his

(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"

L2 11 S L1 AND AMMONIA

=>

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- NEWS 2 JAN 11 STN Express 8.6 Now Available
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- NEWS 4 APR 15 USPATFULL/USPAT2 Now Include Corporate Patent Applicant Information
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- 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
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- NEWS 10 NOV 25 Change to PI field in CPlus 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 CPlus 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.

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=> s "glyceryl tri-[P-phenylbutyrate]"
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          2 "GLYCERYLS"
      27026 "GLYCERYL"
          ("GLYCERYL" OR "GLYCERYLS")
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      189468 "TRIS"
      356204 "TRI"
          ("TRI" OR "TRIS")
      3919888 "P"
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          37 "PHENYLBUTYRATES"
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=> s "glyceryl tri-[4-phenylbutyrate]"
      27025 "GLYCERYL"
          2 "GLYCERYLS"
      27026 "GLYCERYL"
          ("GLYCERYL" OR "GLYCERYLS")

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177002 "TRI"  
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 356204 "TRI"  
 ("TRI" OR "TRIS")  
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=> d 12 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
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, 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				

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



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  $\mu\text{mol/L}$ ;  $C_{\text{max}}$  = 56.3 vs. 79.1  $\mu\text{mol/L}$ ; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time-normalized AUC) by post hoc anal. Systemic exposure (AUC<sub>0-24</sub>) to PBA on GPB was 27% lower than on NaPBA (540 vs. 739  $\mu\text{g h/mL}$ ), whereas exposure to phenylacetic acid (PAA) (575 vs. 596  $\mu\text{g h/mL}$ ) and phenylacetylglutamine (PAGN) (1098 vs. 1133  $\mu\text{g h/mL}$ ) 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 '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 12 and urea

344374 UREA  
14175 UREAS  
348696 UREA  
(UREA OR UREAS)

L3 1 L2 AND UREA

=> d 13

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

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

<b>SERIAL NUMBER</b> 14/958,259	<b>FILING or 371(c) DATE</b> 12/03/2015	<b>CLASS</b> 424	<b>GROUP ART UNIT</b> 1621	<b>ATTORNEY DOCKET NO.</b> HOR0026-201TC2-US		
<b>APPLICANTS</b> Horizon Therapeutics, Inc., Deerfield, IL; <b>INVENTORS</b> Bruce Scharschmidt, San Francisco, CA; Masoud Mokhtarani, Walnut Creek, CA; <b>** CONTINUING DATA *****</b> 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 <b>** FOREIGN APPLICATIONS *****</b> <b>** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **</b> 12/11/2015						
Foreign Priority claimed <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	35 USC 119(a-d) conditions met <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	<input type="checkbox"/> Met after Allowance	<b>STATE OR COUNTRY</b> CA	<b>SHEETS DRAWINGS</b> 3	<b>TOTAL CLAIMS</b> 10	<b>INDEPENDENT CLAIMS</b> 4
<b>ADDRESS</b> GLOBAL PATENT GROUP - HOR 1005 NORTH WARSON ROAD SUITE 404 SAINT LOUIS, MO 63132 UNITED STATES						
<b>TITLE</b> METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS						
<b>FILING FEE RECEIVED</b> 2440	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit		



<b>Search Notes</b>  	<b>Application/Control No.</b>  14958259	<b>Applicant(s)/Patent Under Reexamination</b>  SCHARSCHMIDT ET AL.
	<b>Examiner</b>  SAVITHA RAO	<b>Art Unit</b>  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
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## EAST Search History

## EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
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S2	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:46
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

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S12	4	S11 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15: 14:12
S13	4	((BRUCE) near2 (SCHARSCHMI DT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15: 14:13
S14	9	((BRUCE) near2 (SCHARSCHMI DT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15: 14:13
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S17	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2012/11/16: 07:12
S18	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/16: 07:13
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S22	9	((BRUCE) near2 (SCHARSCHMI DT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20: 10:56
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S24	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20: 10:56
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S28	2	S27 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S29	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S30	4	S29 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S31	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 10:56
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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S35	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2012/12/20 10:56
S36	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 10:56
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S38	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
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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S41	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
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S44	0	S37 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S45	8	S43 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
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
S48	4	S47 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S49	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S50	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
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S53	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2012/12/20 16:43
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S56	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S57	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S58	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
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S62	0	S55 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S63	8	S61 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
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
S66	4	S65 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43

EAST Search History

S67	4	((BRUCE) near2 (SCHARSCHMI DT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S68	9	((BRUCE) near2 (SCHARSCHMI DT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
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S74	64	((BRUCE) near2 (SCHARSCHMI DT)).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

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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
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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
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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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**2/ 1/ 2016 1:12:05 PM**

**H:\ EAST - WKSP\ Workspaces\ 14 applications\ 14816674.wsp**





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Substitute for form 1449/PTO				<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>				<b>Application Number</b>	TBD
(use as many sheets as necessary)				<b>Filing Date</b>	TBD
				<b>First Named Inventor</b>	Bruce Scharschmidt
				<b>Art Unit</b>	TBD
				<b>Examiner Name</b>	TBD
				<b>Attorney Docket Number</b>	HOR0026-201TC2-US
Sheet	1	of	21		

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. 1	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code <sup>2</sup> (if known)			
	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	
	P7	6,219,567	04-17-2001	Cardiox Corporation	
	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	
	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	
	P16	2008/0119554	05-22-2008	Rajiv Jalan et al	
	P17	2010/0008859	01-14-2010	Hyperion Therapeutics, Inc.	
	P18	2010/0016207	01-21-2010	Wurtman, RJ et al	
	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.	

Examiner Signature	Date Considered
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\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Substitute for form 1449/PTO				<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>				<b>Application Number</b>	TBD
				<b>Filing Date</b>	TBD
<i>(use as many sheets as necessary)</i>				<b>First Named Inventor</b>	Bruce Scharschmidt
				<b>Art Unit</b>	TBD
				<b>Examiner Name</b>	TBD
Sheet	2	of	21	<b>Attorney Docket Number</b>	HOR0026-201TC2-US

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
		Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>5</sup> <i>(if known)</i>				
	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.		
	F7	WO2010/025303	03-04-2010	Ucyclyd Pharma, Inc.		
	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).	
	D3	AMODIO, P., et al., "Detection of Minimal Hepatic Encephalopathy: Normalization and Optimization of the Psychometric Hepatic Encephalopathy Score. A Neuropsychological and Quantified EEG Study," J. Hepatol. 49:346-353 (2008).	
	D4	ANDA Notice Letter, Par Pharmaceutical, Inc. to Hyperion Therapeutics, inc.. Re: Glycerol Phenylbutyrate 1.1 gm/ml oral liquid; United States Patent Nos. 8,404,215 and 8,642,012 Notice of Paragraph IV Certification March 12, 2014.	

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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	
	D6	ANDA Notice Letter, Lupin Ltd. to Horizon Therapeutics, Inc.. Re: Notification of Invalidity, Unenforceability, and/or Noninfringement for U.S. Patent No. 9,095,559 Pursuant to § 505(j)(2)(B)(ii) and (iv) of the Federal Food, Drug, and Cosmetic Act, Nov. 6, 2015	
	D7	BAJAJ, J. S., et al., "Review Article: The Design of Clinical Trials in Hepatic Encephalopathy -An International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) Consensus Statement," Aliment Pharmacol Ther. 33 (7):739-747 (2011).	
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	D9	BATSHAW, M.L. et al., "Treatment of Inborn Errors of Urea Synthesis: Activation of Alternative Pathways of Waste Nitrogen Synthesis and Excretion", 306 N. Engl. J. Med. 1387 (1982).	
	D10	BATSHAW, M.L. et al., "New Approaches to the Diagnosis and Treatment of Inborn Errors of Urea Synthesis", 68 Pediatrics 290 (1981).	
	D11	BATSHAW, M.L. et al., "Treatment of Carbamyl Phosphate Synthetase Deficiency with Keto Analogues of Essential Amino Acids", 292 The New England J. Medicine, 1085 (1975)	
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	D13	BATSHAW, M.L., "Hyperammonemia," Current Problems in Pediatrics, Vol 14, Issue 11, pg 6-69 (1984).	
	D14	BATSHAW, M. L. et. al., "Alternative Pathway Therapy for Urea Cycle Disorder: Twenty Years Later", 138 J. Pediatrics S46 (2001).	
	D15	BERRY, G. T. et al., "Long-Term Management of Patients with Urea Cycle Disorders", 138 J. Pediatrics S56 (2001).	

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	D17	BLEI, A. T., et al., "Hepatic Encephalopathy," Am. J. Gastroenterol. 96(7):1968-1976 (2001).	
	D18	BRAHE, C., et al., (2005) "Phenylbutyrate Increases SMN Gene Expression in Spinal Muscular Atrophy Patients," Eur J Hum Genet 13:256-259.	
	D19	BRUNETTI-PIERRI, N., et al., (2011) ""Phenylbutyrate Therapy for Maple Syrup Urine Disease", Hum Mol Genet 20(4):631-640.	
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	D23	BRUSILOW, S.W. "Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion, PEDIATRIC RESEARCH, Vol. 29, No. 2, 147-150 (1991)	
	D24	BRUSILOW, S.W. et al, "Treatment of Urea Cycle Disorders", in TREATMENT OF GENETIC DISEASES 79 (R.J. Desnik. et al., eds.1991).	
	D25	BRUSILOW, S.W. et al., "Restoration of Nitrogen Homeostasis in a Man with Ornithine Transcarbamylase Deficiency", 42 J. Metabolism 1336 (1993).	
	D26	BRUSILOW, S.W., "Protocols for Management of Intercurrent Hyperammonemia in Patients with Urea Cycle Disorders", FDA Application to Market a New Drug for Human Use or an Antibiotic Drug for Human Use. Fourteen pages (Amendment Dated Jul. 25, 1994).	
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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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	D42	CLAY, A. et. al, "Hyperammonemia in the ICU", 132 Chest 1368 (2007).	
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	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.	
	D49	COMTE, B., et al., "Identification of Phenylbutrylglutamine, A New Metabolite of Phenylbutyrate Metabolism in Humans", 37 J. Mass Spectrometry 581 (2002).	
	D50	CONN, H. O., et al., "Liver Physiology and Disease: Comparison of Lactulose and Neomycin in the Treatment of Chronic Portal-Systemic Encephalopathy. A Double Blind Controlled Trial," Gastroenterology 72(4):573-583 (1977).	
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	D55	DEFERRARI, G. et al., "Brain Metabolism of Amino Acids and Ammonia in Patients with Chronic Renal Insufficiency", 20 Kidney International 505 (1981).	
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	D64	European Medicines Agency, European Public Assessment Report: Summary for the Public for Ammonaps (2009).	
	D65	European Medicines Agency, Scientific Discussion for Ammonaps (2005).	
	D66	European Medicines Agency, Scientific Discussion for Carbaglu (2004).	
	D67	EUROPEAN PATENT OFFICE, Extended European Search Report for EP09739263 completed November 2, 2011.	
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	D69	Examination Report mailed Feb. 5, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on Aug. 27, 2009, two pages.	
	D70	Examination Report mailed May 11, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on Aug. 27, 2009, one page.	
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	D74	FDA Label for Buphenyl, six pages.	
	D75	FDA Buphenyl® (Sodium Phenylbutyrate) Label, nine pages. (Aug. 2003).	

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\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO				<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>				<b>Application Number</b>	TBD
<i>(use as many sheets as necessary)</i>				<b>Filing Date</b>	TBD
Sheet 20 of 21				<b>First Named Inventor</b>	Bruce Scharschmidt
				<b>Art Unit</b>	TBD
				<b>Examiner Name</b>	TBD
				<b>Attorney Docket Number</b>	HOR0026-201TC2-US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	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 <sup>6</sup>
	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.	
	D210	VILSTRUP, H., et al., "Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver," Hepatology 60 (2):715-735 (2014).	
	D211	WALSH et al., Chemical Abstract vol. 112, No. 231744	
	D212	WALSH et al., THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 8, pp. 4374-4381 (1990), "sn-1,2-Diacylglycerol Kinase of Escherichia coli".	
	D213	WATERLOW, J.C., The Partition of Nitrogen in the Urine of Malnourished Jamaican Infants, 12 Am. J. of Clin. Nutrition 235 (1963).	
	D214	WELBOURNE, T. et al., "The Effect of Glutamine Administration on Urinary Ammonium Excretion in Normal Subjects and Patients with Renal Disease", 51 J. Clin. Investigation 1852 (1972).	
	D215	WICKEN, B., "Problems in the Management of Urea Cycle Disorders", 81 Molecular Genetics and Metabolism 85 (2004).	
	D216	WILSON, C.J., et al., "Plasma Glutamine and Ammonia Concentrations in Ornithine Carbamoyltransferase Deficiency and Citrullinaemia", 24 J. Inherited Metabolic Disease 691 (2001).	
	D217	WRIGHT, G., et al., "Management of Hepatic Encephalopathy", 2011 International Journal of Hepatology 1 (2011).	
	D218	WRIGHT, P., Review: "Nitrogen Excretion: Three End Products, Many Physiological Roles", 198 J. Experimental Biology 273 (1995).	

Examiner Signature	Date Considered
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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>				<b>Application Number</b>	TBD
<i>(use as many sheets as necessary)</i>				<b>Filing Date</b>	TBD
Sheet 21 of 21				<b>First Named Inventor</b>	Bruce Scharschmidt
				<b>Art Unit</b>	TBD
				<b>Examiner Name</b>	TBD
				<b>Attorney Docket Number</b>	HOR0026-201TC2-US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	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 <sup>6</sup>
	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	
	D220	YAJIMA, et al. "Diurnal Fluctuations of Blood Ammonia Levels in Adult-Type Citrullinemia", 137 Tokohu J. Ex/ Med, 213-220 (1982)	
	D221	YU, Ryan and Potter, Murray, "Diagnosis of Urea Cycle Disorders in Adulthood: Late- Onset Carbamyl Phosphate Synthetase 1 Deficiency", 7 MUMJ 30 (2010).	
	D222	YUDKOFF, M. et al., "In Vivo Nitrogen Metabolism in Ornithine Transcarbamylase Deficiency", 98 J. Clin. Invest. 2167 (1996).	
	D223	ZEITLIN, P., "Novel Pharmacologic Therapies for Cystic Fibrosis", 103 J. Clinical Investigation 447 (1999).	
	D224	ZEITLIN, P.L. et al., "Evidence of CFTR Function in Cystic Fibrosis After System Administration of 4-Phenylbutyrate", 6 Mol. Therapy 119 (2002).	

Examiner Signature	/SAVITHA M RAO/	Date Considered	02/01/2016
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If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

Scharschmidt *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  $\mu\text{mol/L}$ .

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  $\mu\text{mol/L}$ .

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  $\mu\text{mol/L}$ .

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.

Attorney Docket No. HOR0026-201TC2-US

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

<b>EFS ID:</b>	24946500
<b>Application Number:</b>	14958259
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	3046
<b>Title of Invention:</b>	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
<b>First Named Inventor/Applicant Name:</b>	Bruce Scharschmidt
<b>Customer Number:</b>	101325
<b>Filer:</b>	Brock D. Levin/Vicki Truman
<b>Filer Authorized By:</b>	Brock D. Levin
<b>Attorney Docket Number:</b>	HOR0026-201TC2-US
<b>Receipt Date:</b>	18-FEB-2016
<b>Filing Date:</b>	03-DEC-2015
<b>Time Stamp:</b>	11:08:06
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	no
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### File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		20160218_Response1.pdf	51991 <small>583f4c7ca02e9fc177956432c9a14eafc669994c</small>	yes	6

<b>Multipart Description/PDF files in .zip description</b>		
<b>Document Description</b>	<b>Start</b>	<b>End</b>
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	6
<b>Warnings:</b>		
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<b>Total Files Size (in bytes):</b>	51991	
<p>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.</p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  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.</p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  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.</p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  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.</p>		

<b>Doc Code: DIST.E.FILE</b> <b>Document Description: Electronic Terminal Disclaimer - Filed</b>		PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce
Electronic Petition Request	<b>TERMINAL DISCLAIMER TO OBLIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT</b>	
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	
<input checked="" type="checkbox"/> Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action <input checked="" type="checkbox"/> 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)  9095559 8642012 8404215 9254278		

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

<b>Application Number:</b>	14958259			
<b>Filing Date:</b>	03-Dec-2015			
<b>Title of Invention:</b>	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS			
<b>First Named Inventor/Applicant Name:</b>	Bruce Scharschmidt			
<b>Filer:</b>	Brock D. Levin/Vicki Truman			
<b>Attorney Docket Number:</b>	HOR0026-201TC2-US			
Filed as Large Entity				
<b>Filing Fees for Utility under 35 USC 111(a)</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
Statutory or Terminal Disclaimer	1814	1	160	160
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Extension-of-Time:</b>				
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>160</b>

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

<b>EFS ID:</b>	24946661
<b>Application Number:</b>	14958259
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	3046
<b>Title of Invention:</b>	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
<b>First Named Inventor/Applicant Name:</b>	Bruce Scharschmidt
<b>Customer Number:</b>	101325
<b>Filer:</b>	Brock D. Levin/Vicki Truman
<b>Filer Authorized By:</b>	Brock D. Levin
<b>Attorney Docket Number:</b>	HOR0026-201TC2-US
<b>Receipt Date:</b>	18-FEB-2016
<b>Filing Date:</b>	03-DEC-2015
<b>Time Stamp:</b>	11:17:29
<b>Application Type:</b>	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 a952d31d7f56a62cf4ff46dfb39030e6e01612f	no	3

**Warnings:**

**Information:**

2	Fee Worksheet (SB06)	fee-info.pdf	30603 1acbd7371a59916f79f59deae7e5ddb8143ae498	no	2
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**Warnings:**

**Information:**

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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.

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.

<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875	Application or Docket Number <b>14/958,259</b>	Filing Date <b>12/03/2015</b>	<input type="checkbox"/> To be Mailed
---	---	----------------------------------	---------------------------------------

ENTITY:  LARGE  SMALL  MICRO

**APPLICATION AS FILED – PART I**

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (j), or (m))	N/A	N/A	N/A	
<input type="checkbox"/> 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 \$ =	
<input type="checkbox"/> 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).			
<input type="checkbox"/> 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**

	(Column 1)	(Column 2)	(Column 3)	(Column 4)	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT	<b>02/18/2016</b>	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	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
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					
					TOTAL ADD'L FEE	<b>0</b>

	(Column 1)	(Column 2)	(Column 3)	(Column 4)	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
	<input type="checkbox"/> 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/

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.



UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

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

Table with 5 columns: 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

Table with 7 columns: 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 Schar Schmidt	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, 1 \_\_\_\_\_
- (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. 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
- Applicant asserting small entity status. See 37 CFR 1.27
- Applicant changing to regular undiscounted fee status.

**NOTE:** Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

**NOTE:** If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

**NOTE:** Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature \_\_\_\_\_ Date \_\_\_\_\_  
 Typed or printed name \_\_\_\_\_ Registration No. \_\_\_\_\_



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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.

101325 7590 03/08/2016
GLOBAL PATENT GROUP - HOR
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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.

<b>Notice of Allowability</b>	<b>Application No.</b> 14/958,259	<b>Applicant(s)</b> SCHARSCHMIDT ET AL.	
	<b>Examiner</b> SAVITHA RAO	<b>Art Unit</b> 1621	<b>AIA (First Inventor to File) Status</b> 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](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto: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)**

- |  |  |
|--|--|
| <ol style="list-style-type: none"> <li>1. <input type="checkbox"/> Notice of References Cited (PTO-892)</li> <li>2. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),<br/>Paper No./Mail Date _____</li> <li>3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit<br/>of Biological Material</li> <li>4. <input type="checkbox"/> Interview Summary (PTO-413),<br/>Paper No./Mail Date _____.</li> </ol> | <ol style="list-style-type: none"> <li>5. <input type="checkbox"/> Examiner's Amendment/Comment</li> <li>6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance</li> <li>7. <input type="checkbox"/> Other _____.</li> </ol> |
|--|--|

/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
S2	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:46
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
S7	18	("20040229948"   "20060135612"   "4284647"   "6083984"   "20080119554"   "6219567"   "20100008859"   "6050510"   "5968979"   "20100008859"   "6219567").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:57
S8	0	S1 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
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			
S12	4	S11 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:12
S13	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 14:13
S14	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 14:13
S15	18	("4284647"   "6083984"   "6050510"   "6219567"   "20040229948"   "20080119554"   "20060135612"   "5968979"   "20100008859").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/16 07:11
S16	2	S15 and "nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/16 07:11
S17	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2012/11/16 07:12
S18	9	((Saul) near2 (Bruslow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/16 07:13
S19	0	"13417137".rlan. or ("13".src. and "417137".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S20	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 10:56
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
S23	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 10:56
S24	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 10:56
S25	18	("20040229948"   "20060135612"   "4284647"   "6083984"   "20080119554"   "6219567"   "20100008859"   "6050510"   "5968979"   "20100008859"	US-PGPUB; USPAT; USOCR; FPRS;	OR	OFF	2012/12/20 10:56

		"6219567").PN.	EPO; JPO; DERWENT; IBM_TDB			
S26	0	S19 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S27	8	S25 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S28	2	S27 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S29	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S30	4	S29 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S31	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 10:56
S32	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 10:56
S33	18	("4284647"   "6083984"   "6050510"   "6219567"   "20040229948"   "20080119554"   "20060135612"   "5968979"   "20100008859").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S34	2	S33 and "nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 10:56
S35	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2012/12/20 10:56
S36	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 10:56
S37	0	"13417137".rlan. or ("13".src. and "417137".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S38	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
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

			USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			
S41	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S42	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
S43	18	("20040229948"   "20060135612"   "4284647"   "6083984"   "20080119554"   "6219567"   "20100008859"   "6050510"   "5968979"   "20100008859"   "6219567").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
S44	0	S37 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S45	8	S43 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
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
S48	4	S47 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S49	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S50	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
S51	18	("4284647"   "6083984"   "6050510"   "6219567"   "20040229948"   "20080119554"   "20060135612"   "5968979"   "20100008859").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S52	2	S51 and "nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43

S53	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2012/12/20 16:43
S54	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S55	0	"13417137".rlan. or ("13".src. and "417137".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S56	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S57	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S58	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
S59	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S60	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
S61	18	("20040229948"   "20060135612"   "4284647"   "6083984"   "20080119554"   "6219567"   "20100008859"   "6050510"   "5968979"   "20100008859"   "6219567").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
S62	0	S55 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S63	8	S61 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
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
S66	4	S65 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43

S67	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S68	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
S69	18	("4284647"   "6083984"   "6050510"   "6219567"   "20040229948"   "20080119554"   "20060135612"   "5968979"   "20100008859").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S70	2	S69 and "nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S71	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2012/12/20 16:43
S72	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/20 16:43
S73	0	"14816674".rlan. or ("14".src. and "816674".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/10/28 17:33
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**









<b>Search Notes</b>  	<b>Application/Control No.</b>  14958259	<b>Applicant(s)/Patent Under Reexamination</b>  SCHARSCHMIDT ET AL.
	<b>Examiner</b>  SAVITHA RAO	<b>Art Unit</b>  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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Table with 4 columns: APPLICATION NUMBER (14/958,259), FILING OR 371(C) DATE (12/03/2015), FIRST NAMED APPLICANT (Bruce Scharschmidt), ATTY. DOCKET NO./TITLE (HOR0026-201TC2-US)

CONFIRMATION NO. 3046

PUBLICATION NOTICE

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



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

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

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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

**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.

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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 Schar Schmidt	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, 1 \_\_\_\_\_
- (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. 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)

**Horizon Therapeutics, Inc.**

**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

4a. The following fee(s) are submitted:

- Issue Fee
- Publication Fee (No small entity discount permitted)
- Advance Order - # of Copies \_\_\_\_\_

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- A check is enclosed.
- Payment by credit card. Form PTO-2038 is attached.
- The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 50-4297 (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- Applicant certifying micro entity status. See 37 CFR 1.29
- Applicant asserting small entity status. See 37 CFR 1.27
- Applicant changing to regular undiscounted fee status.

**NOTE:** Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

**NOTE:** If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

**NOTE:** Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature /Brock Levin/

Date March 28, 2016

Typed or printed name Brock Levin

Registration No. 65,040

## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>	14958259			
<b>Filing Date:</b>	03-Dec-2015			
<b>Title of Invention:</b>	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS			
<b>First Named Inventor/Applicant Name:</b>	Bruce Scharschmidt			
<b>Filer:</b>	Brock D. Levin/Valerie Lechner			
<b>Attorney Docket Number:</b>	HOR0026-201TC2-US			
Filed as Large Entity				
<b>Filing Fees for Utility under 35 USC 111(a)</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
Utility Appl Issue Fee	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Extension-of-Time:</b>				
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>960</b>

## Electronic Acknowledgement Receipt

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

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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
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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.**



Receipt date: 12/03/2015

14958259 - GAU: 1621

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

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Substitute for form 1449/PTO				<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>				<b>Application Number</b>	TBD
<i>(use as many sheets as necessary)</i>				<b>Filing Date</b>	TBD
Sheet 1 of 21				<b>First Named Inventor</b>	Bruce Scharschmidt
				<b>Art Unit</b>	TBD
				<b>Examiner Name</b>	TBD
				<b>Attorney Docket Number</b>	HOR0026-201TC2-US

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. 1	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code <sup>2</sup> (if known)			
Change(s) applied to document, /V.D.W./ 3/10/2016	P1	4,284,647	08-18-1981	<del>The Johns Hopkins University</del>	Brusilow et al.
	P2	4,457,942	07-03-1984	Brusilow, S.W.	
	P3	5,654,333	08-05-1997	<del>The United States Of America As Represented By The Department Of Health And Human Services</del>	Samid
	P4	5,968,979	10-19-1999	<del>Brusilow Enterprises Llc</del>	
	P5	6,060,510	05-09-2000	<del>Brusilow Enterprises Llc</del>	
	P6	6,083,984	07-04-2000	<del>Brusilow Enterprises Llc</del>	
	P7	6,219,567	04-17-2001	<del>Cardiox Corporation</del>	Eggers et al.
	P8	8,094,521	01-10-2012	<del>Nightongale Products LLC</del>	Levy
	P9	8,404,215	03-26-2013	<del>Hyperion Therapeutics, Inc.</del>	Scharschmidt et al.
	P10	8,642,012	02-04-2014	<del>Hyperion Therapeutics, Inc.</del>	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	<del>U.S. Department Of Veterans Affairs</del>	Ferrante
P16	2008/0119554	05-22-2008	Rajiv Jalan et al		
P17	2010/0008859	01-14-2010	<del>Hyperion Therapeutics, Inc.</del>	Scharschmidt	
P18	2010/0016207	01-21-2010	Wurtman, RJ et al		
P19	2012/0022157	01-26-2012	<del>Joyold Pharma, Inc.</del>	Scharschmidt	
P20	2012/0220661	08-30-2012	<del>Baylor College of Medicine</del>	Lee	
P21	2013/0210914	08-15-2013	<del>Hyperion Therapeutics, Inc.</del>	Scharschmidt et al.	
P22	2013/0281530	10-24-2013	Scharschmidt, et al		
P23	2014/0142186	05-22-2014	<del>Hyperion Therapeutics, Inc.</del>	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, /V.D.W./ 3/10/2016

Change(s) applied to document,

/S.H./ 4/5/2016

Examiner Signature	Date Considered
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\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 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.

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4835-0776-7055.1

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



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Table with 5 columns: 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):

Horizon Therapeutics, Inc., Deerfield, IL;
Bruce Scharschmidt, San Francisco, CA;
Masoud Mokhtarani, Walnut Creek, CA;

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