Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

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

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

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

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

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

3. The applicable box is checked below:

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

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

---OR---

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

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

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

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

Signature /Lauren L. STEVENS/	Date 7-31-2015
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.

LUPIN EX. 1022

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HOR0026-201-C1US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

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

Secrecy Order 37 CFR 5.2

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

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bruce		Scharschmidt	

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

City	San Francisco	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	45 St. Francis Boulevard		
Address 2			
City	San Francisco	State/Province	CA
Postal Code	94127	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Masoud		Mokhtarani	

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

City	Walnut Creek	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	725 Castle Rock Road		
Address 2			
City	Walnut Creek	State/Province	CA
Postal Code	94598	Country i	US

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

Correspondence Information:

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HOR0026-201-C1US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

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

Application Information:

Title of the Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS		
Attorney Docket Number	HOR0026-201-C1US	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	3	**Suggested Figure for Publication (if any)**	

Filing By Reference :

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

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

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

Publication Information:

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

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

Representative Information:

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

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	101325		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HOR0026-201-C1US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

Domestic Benefit/National Stage Information:

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

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13775000	2013-02-22

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13775000	Continuation of	13417137	2012-03-09	8404215	2013-03-26

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13417137	Claims benefit of provisional	61542100	2011-09-30

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13417137	Claims benefit of provisional	61564668	2011-11-29

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

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

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

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HOR0026-201-C1US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

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

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

Authorization to Permit Access:

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

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HOR0026-201-C1US
	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

Applicant 1 Remove

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor :	
If the Applicant is an Organization check here.	☒
Organization Name	Horizon Therapeutics, Inc.

Mailing Address Information:

Address 1	520 Lake Cook Road		
Address 2	Suite 520		
City	Deerfield	**State/Province**	IL
Country [i]	US	Postal Code	60015
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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Assignee 1

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

Remove

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

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	Application Number	
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

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

Mailing Address Information For Assignee including Non-Applicant Assignee:

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

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

Signature:

Remove

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

Signature	/Lauren L. STEVENS/			Date (YYYY-MM-DD)	2015-07-31
First Name	Lauren	Last Name	Stevens	Registration Number	36691

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

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

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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 the Freedom of Information Act requires disclosure of these records.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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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 inspections 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.

METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

RELATED APPLICATIONS

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

BACKGROUND

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

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

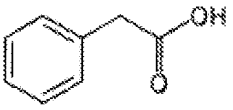
[0004] Hepatic encephalopathy (HE) refers to a spectrum of neurologic signs and symptoms believed to result from hyperammonemia, which frequently occur in subjects with cirrhosis or

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

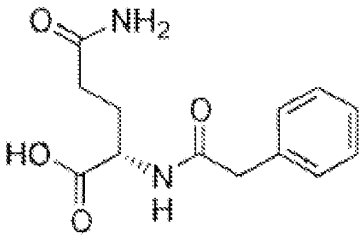
[0005] Subjects with nitrogen retention disorders whose ammonia levels and/or symptoms are not adequately controlled by dietary restriction of protein and/or dietary supplements are generally treated with nitrogen scavenging agents such as sodium phenylbutyrate (NaPBA, approved in the United States as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

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

phenylbutyrate



Phenylacetic acid



Phenylacetylglutamine

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

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

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

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

SUMMARY

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

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

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

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

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

BRIEF DESCRIPTION OF DRAWINGS

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

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

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

DETAILED DESCRIPTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Examples

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

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

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

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

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

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

[0065] Exploratory analysis:

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

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

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

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

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

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

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

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

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

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

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

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

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

5) Cmax [0-100] μmol/L.

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

1) [0-0.5*ULN];

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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11. Thibault Cancer 75:2932 (1995)

What is claimed is:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6. The method of claim 3, further comprising:

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

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

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

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

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

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

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

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

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

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

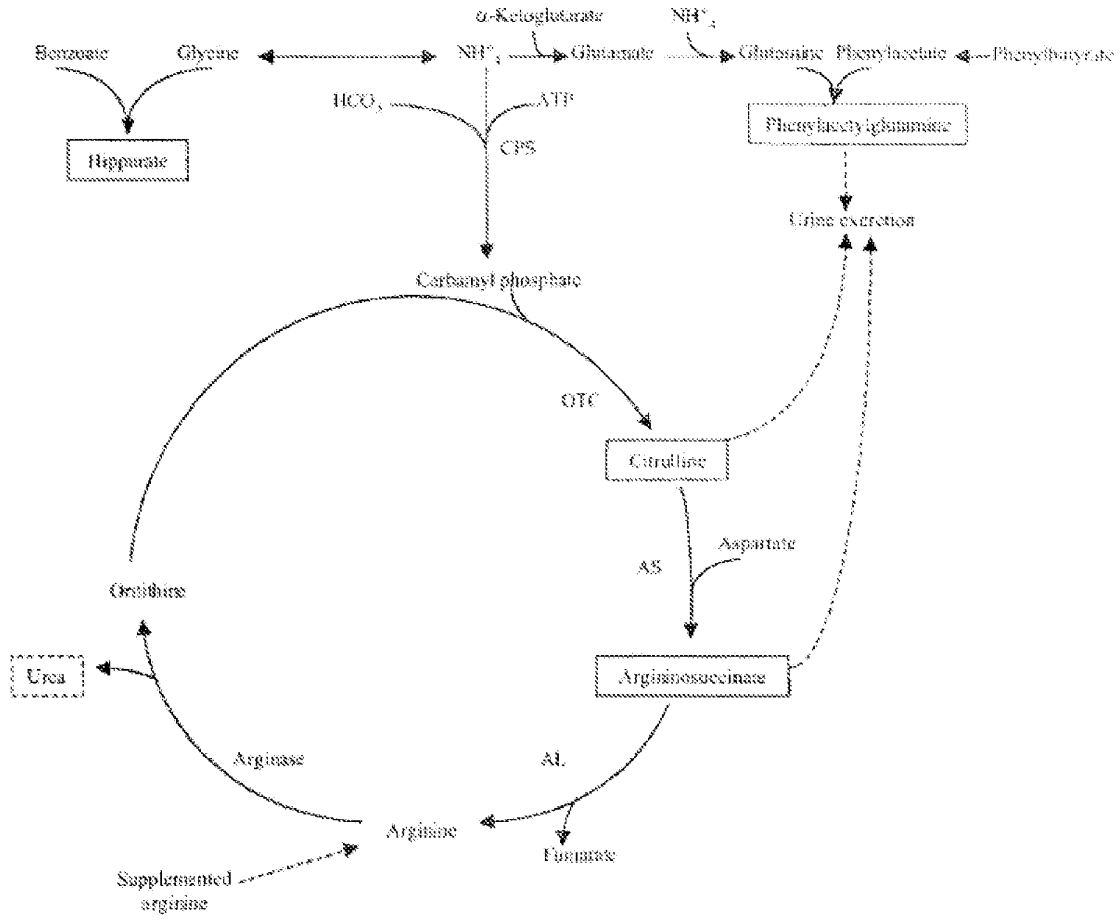
(i) determining a target urinary phenylacetyl glutamine (PAGN) output; and

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

ABSTRACT

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

Figure 1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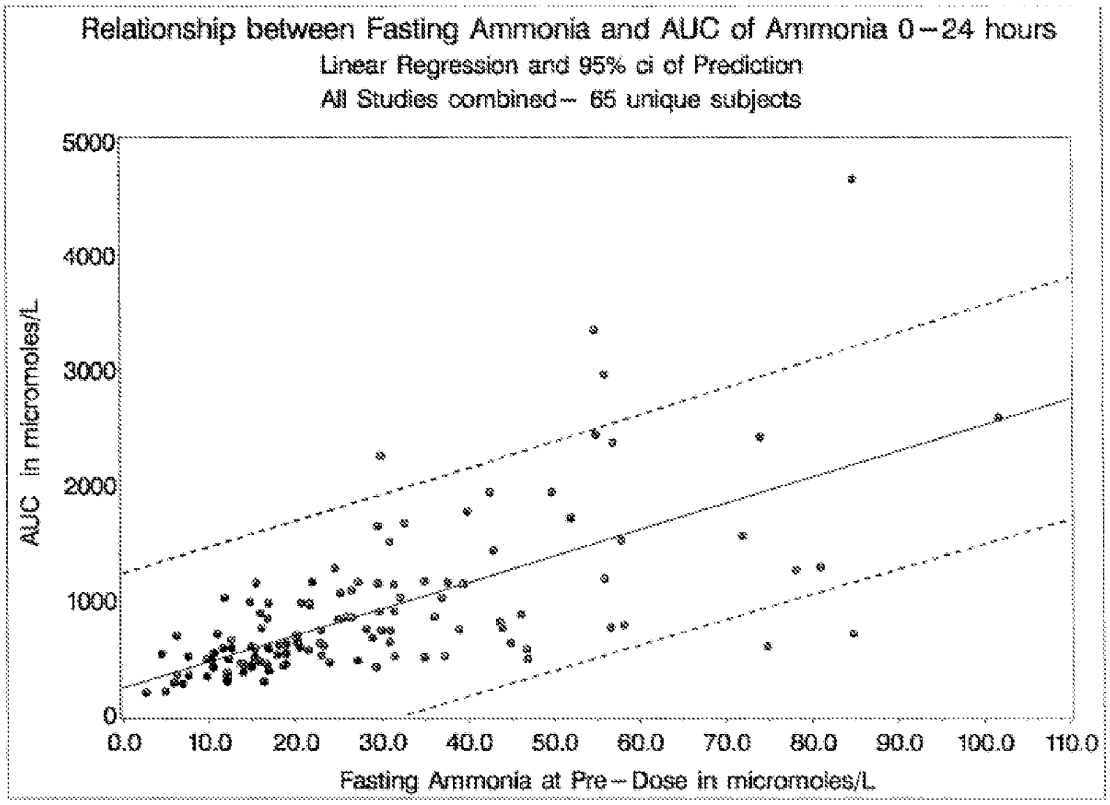
NH^+_4
Benzoate
Glycine
NH^+_4
Glutamate
Glutamine
Phenylacetate
Phenylbutyrate
HCO_3
ATP
Hippurate
CPS
Phenylacetylglutamine
Urine excretion
Carbamyl phosphate
OTC
Citrulline
Aspartate
AS
Ornithine
Urea
Argininosuccinate
Arginase
AL
Arginine
Fumarate
Supplemented arginine

Figure 2


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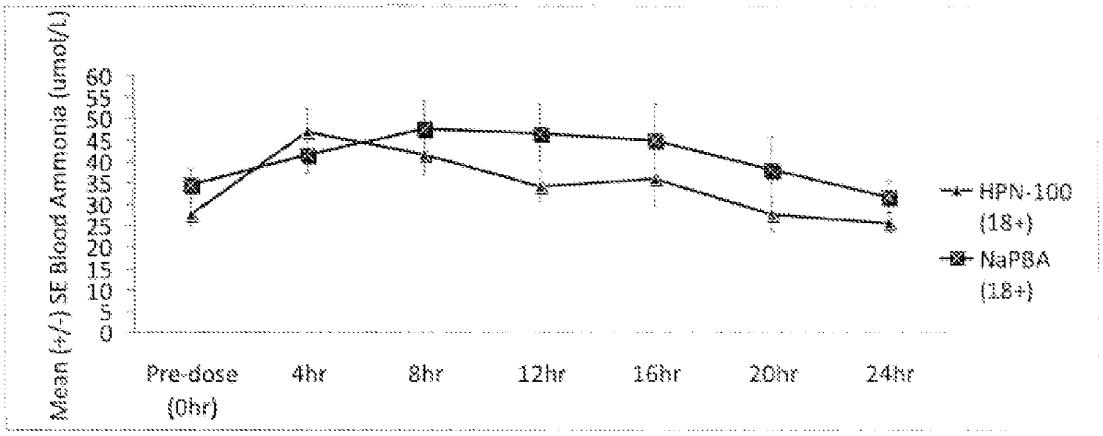
4000
3000
2000
1000
0
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
Fasting Ammonia at Pre – Dose in micromoles/L

Figure 3

A.


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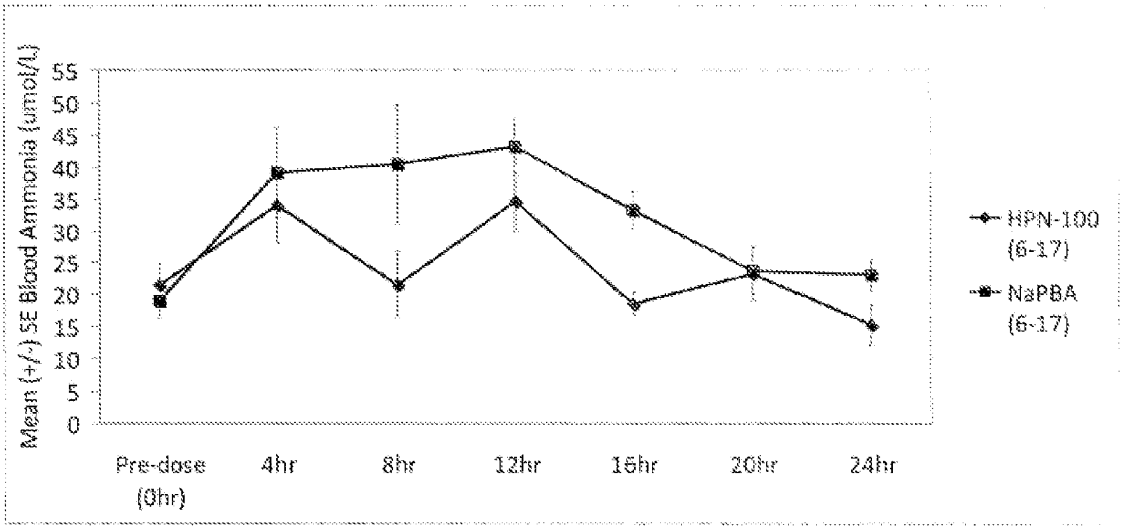
55
50
45
40
35
30
25
20
15
10
5
0
Pre-dose (0hr)
4hr
8hr
12hr
16hr
20hr
24hr
HPN-100 (18+)
NaPBA (18+)

B.


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

Atty Docket No.: HOR0026-201C1-US

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Title: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

NOTICE OF RELATED LITIGATION

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

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

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

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

divisional 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

Attorney Docket No.: HOR0026-201C1-US

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Title: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.561

ELECTRONICALLY VIA EFS-WEB

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

Sir:

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

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

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

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

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

Respectfully submitted,

By /Lauren L. STEVENS/

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: March 12, 2012

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Sheet 1 of 13

Complete if Known	
Application Number	To Be Assigned
Filing Date	TBA
First Named Inventor	Bruce Scharschmidt
Art Unit	TBA
Examiner Name	TBA
Attorney Docket Number	HOR0026-201C1-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication or Issue Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	P2	5,654,333	08-05-1997	The United States Of America As Represented By The Department Of Health And Human Services	
	P3	8,094,521	01-10-2012	Nightengale Products LLC	
	P4	8,404,215	03-26-2013	Hyperion Therapeutics, Inc.	
	P5	2003/0195255	10-16-2003	Marshall L. Summar	
	P6	2005/0273359	12-08-2005	Young, D.E.	
	P7	2010/0016207	01-21-2010	Wurtman, RJ et al	
	P8	2013/0281530	10-24-2013	Scharschmidt, B et al	
	P9	2014/0142186	05-22-2014	Hyperion Therapeutics, Inc.	
	P10	6,219,567	4/17/2001	EGGERS	
	P11	8,642,012	2/4/2014	SCHARSCHMIDT	
	P12	2010/0008859	1/14/2010	SCHARSCHMIDT	
	P13	2012/0022157	1/26/2012	SCHARSCHMIDT	
	P14	9,078,865	7/14/2015	LEE	
	P15	2013/0210914	8/15/2013	SCHARSCHMIDT	
	P16	2008/0119554	5/22/2008	JALAN	

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

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FOREIGN PATENT DOCUMENTS

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	F1	WO1994/22494	10-13-1994	The DuPont Merck Pharmaceutical Company		
	F2	WO2013/048558	04-04-2013	Hyperion Therapeutics, Inc.		
	F3	WO2013/158145	10-24-2013	Hyperion Therapeutics, Inc.		
	F4	WO2007/005633				
	F5	WO2009/087474	7/16/2009	Akthelia Pharmaceuticals		
	F6	WO2012/028620				

NON PATENT LITERATURE DOCUMENTS

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Sheet 3 of 13

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Art Unit	TBA
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Attorney Docket Number	HOR0026-201C1-US

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Date Submitted: March 12, 2012				**First Named Inventor**	Bruce Scharschmidt
				Art Unit	TBA
(use as many sheets as necessary)				**Examiner Name**	TBA
Sheet	4	of	13	**Attorney Docket Number**	HOR0026-201C1-US

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	D43	International Search Report and Written Opinion for PCT/US09/30362, mailed Mar. 2, 2009, 8 pages.	
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(use as many sheets as necessary)				**Art Unit**	TBA
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Sheet	13	of	13	**Attorney Docket Number**	HOR0026-201C1-US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D126	Examination Report for British Patent Application No. GB1013468.2 dated October 28, 2011.	
	D127	International Preliminary Report on Patentability (Ch I) for PCT/US2012/028620 completed June 4, 2012 and mailed on April 10, 2014.	
	D128	International Preliminary Report on Patentability (Ch II) for PCT/US2012/028620, completed August 22, 2013 and mailed September 4, 2013.	
	D129	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion for PCT/US2009/030362 mailed March 2, 2009.	
	D130	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion for PCT/US2012/028620 mailed June 20, 2012.	
	D131	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion for PCT/US2012/54673 mailed November 20, 2012.	
	D132	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion for PCT/US2013/71333 mailed March 28, 2014.	
	D133	LICHTER-KONECKI, U., et al., "Ammonia Control in Children with Urea Cycle Disorders (UCDs); Phase 2 Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate,", Mol. Genet. Metab. 103:323-329 (2011).	

Examiner Signature		Date Considered	

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

Attorney Docket No.: HOR0026-201C1-US

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Title: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

PRELIMINARY AMENDMENT UNDER 37 CFR 1.115

ELECTRONICALLY VIA EFS-WEB

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

Sir:

Prior to examination of the present Application, Applicants respectfully request that the application be amended as follows:

Amendments to the Specification begin on page 2 of this document.

Amendments to the Drawings being on page 3 of this document.

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

Remarks/Arguments begin following the Amendments to the Claims.

Amendments to the Specification

Please amend paragraph [001] as follows:

[0001] The present application is a continuation of U.S. Patent Application 13/775,000, which is now pending, 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

Attached replacement FIG. 1, FIG. 2, and FIG. 3 should replace original FIG. 1, FIG. 2., and FIG 3, respectively.

Amendments to the Claims

This listing of claims replaces all prior versions, and listings, of claims in the present application.

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.

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

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

Remarks

Applicant submits herewith replacement figures. The specification has been amended to update the priority paragraph. No new matter has been added.

Claims 1-11 have been cancelled herein without prejudice or disclaimer. Claims 12-114 have been added. With entry of this amendment, claims 12-14 are pending.

Applicant respectfully requests that the foregoing amendments be made prior to examination of the present application. Applicant believes that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested. If new issues of patentability are raised, the Examiner is invited to call or email the undersigned and arrange for an opportunity to discuss these issues.

Respectfully submitted,

By /Lauren L. STEVENS/

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

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

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

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

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

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

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

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

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

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

LEGAL NAME OF INVENTOR: **Masoud Mokhtarani**

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

Perkins Coie

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

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

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: **Bruce Scharschmidt**

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

Perkins Coie

Figure 1

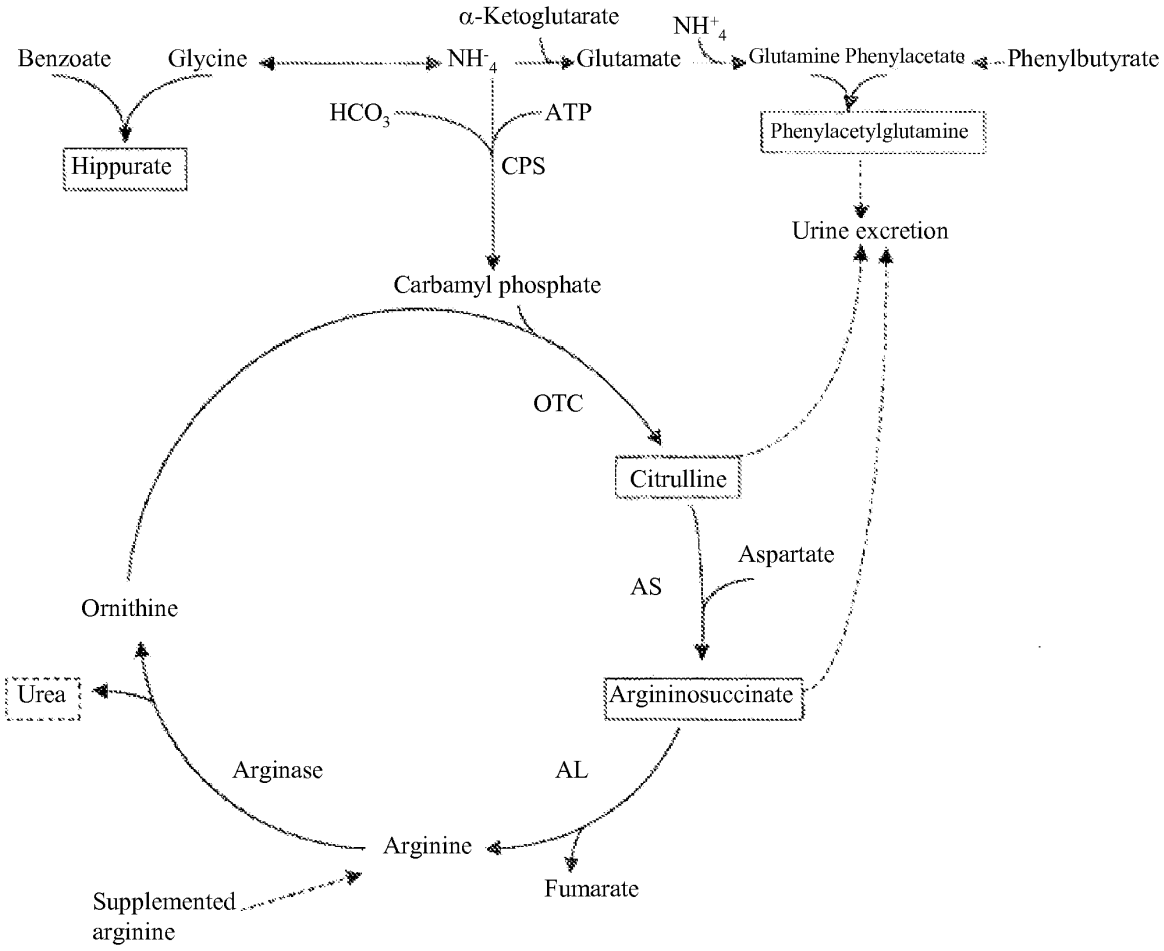

α-Ketoglutarate
NH^+_4
Benzoate
Glycine
NH^-_4
Glutamate
Glutamine
Phenylacetate
Phenylbutyrate
HCO_3
ATP
CPS
Hippurate
Phenylacetylglutamine
Urine excretion
Carbamyl phosphate
OTC
Citrulline
Aspartate
AS
Ornithine
Urea
Argininosuccinate
Arginase
AL
Arginine
Fumarate
Supplemented arginine

Figure 2

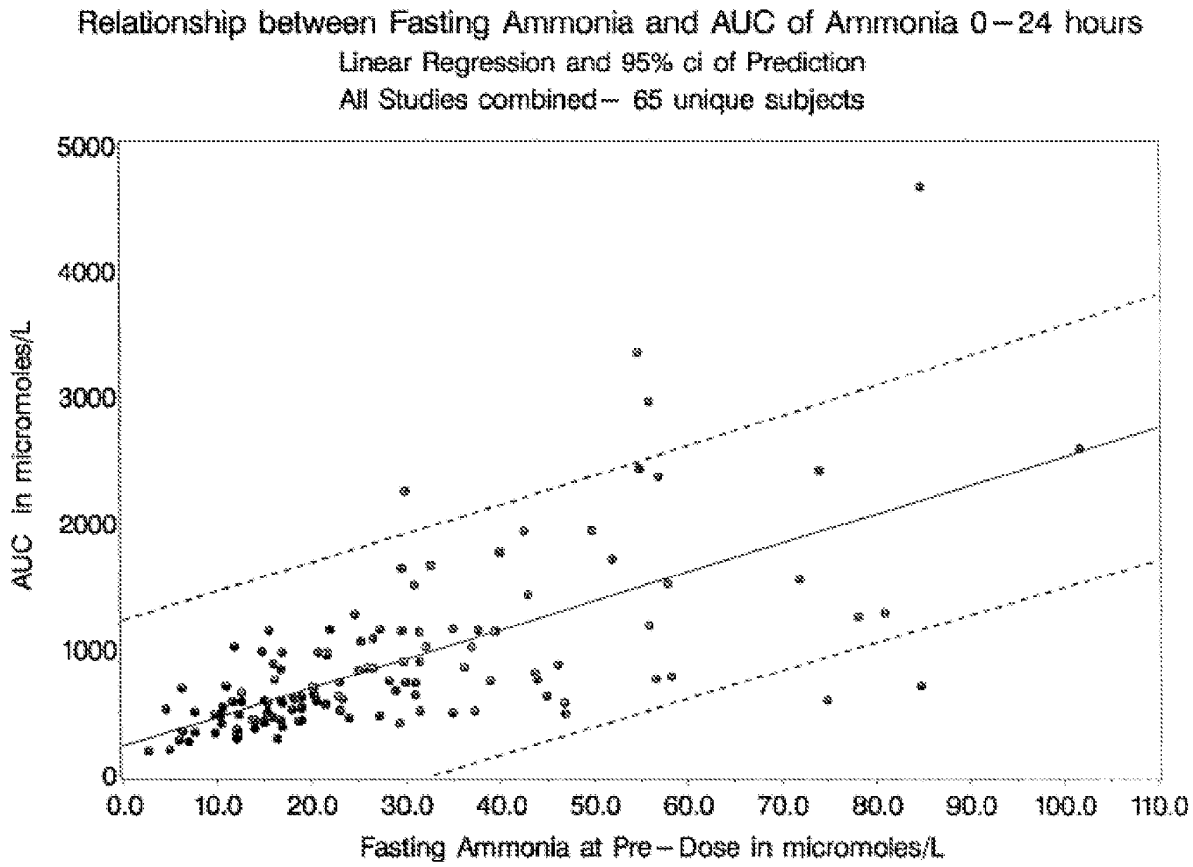
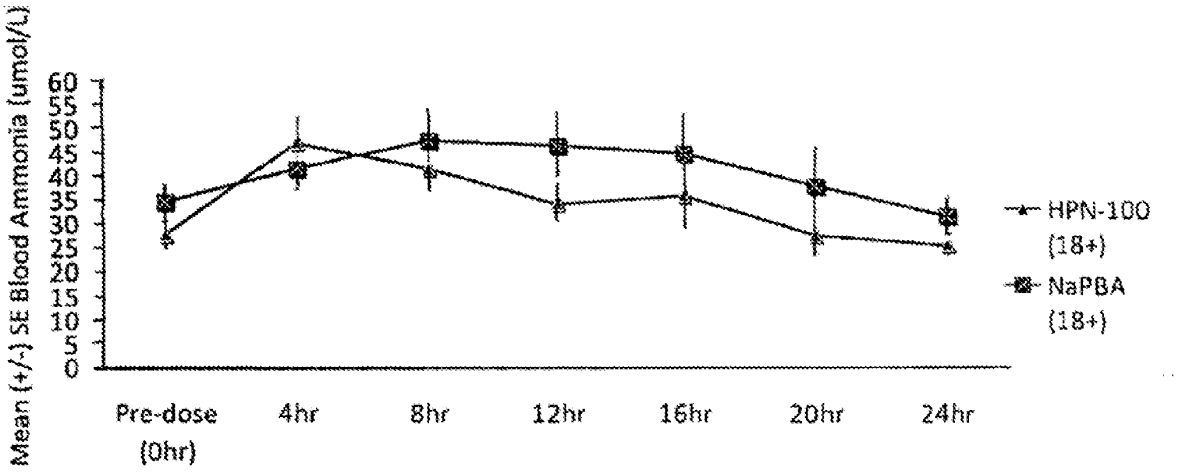
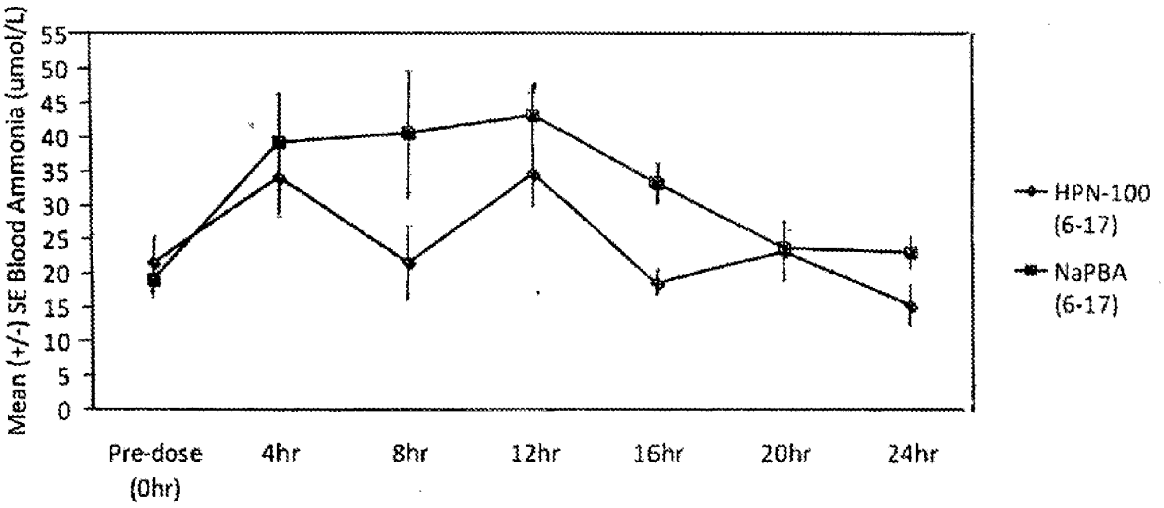

Relationship between Fasting Ammonia and AUC of Ammonia 0 – 24 hours
Linear Regression and 95% ci of Prediction
All Studies combined – 65 unique subjects
AUC in micromoles/L
5000
4000
3000
2000
1000
0
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
Fasting Ammonia at Pre – Dose in micromoles/L

Figure 3

A.


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

B.


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

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Lauren Stevens/Vicki Truman
Attorney Docket Number:	HOR0026-201C1-US

Filed as Large Entity

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

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**5740**

Electronic Acknowledgement Receipt	
EFS ID:	23097643
Application Number:	14816674
International Application Number:	
Confirmation Number:	9599
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Lauren Stevens/Vicki Truman
Filer Authorized By:	Lauren Stevens
Attorney Docket Number:	HOR0026-201C1-US
Receipt Date:	03-AUG-2015
Filing Date:	
Time Stamp:	16:29:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$5740
RAM confirmation Number	3328
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	TrackOne Request	20150803_Track_1_Request.pdf	113868 219dde02a4cfa0004bcd0b2b32dc294f155e9e6d	no	2
Warnings:					
Information:					
2	Application Data Sheet	20150803_ADS.pdf	1561589 807abe202d6670b6c0080bd52b6f5c85ecbf2f0a	no	7
Warnings:					
Information:					
3		20150803_Application.pdf	402212 359f789338e8b148193488d0084a2a451c1b3ca0	yes	38

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	32
Claims	33	34
Abstract	35	35
Drawings-only black and white line drawings	36	38

Warnings:					
Information:					
4	Miscellaneous Incoming Letter	20150803_Notice_Related_Litigation.pdf	19009 aaa751fec04c2c0754f32ed0f9656b9913d322ec	no	2
Warnings:					
Information:					
5	Transmittal Letter	20150803_IDS_Trans.pdf	19688 b01dd700424c5f2f17821a493b092c1ff481ace4	no	2
Warnings:					
Information:					

6	Information Disclosure Statement (IDS) Form (SB08)	20150803_IDS.pdf	193128 f24fe0830369d39fdfbf97079f59ad1250b90320	no	13
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
7		20150803_Preliminary_Amendment.pdf	33561 caf9e75bfcc5e5f5fce13e081c3b289cab600950	yes	5

	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	4
	Applicant Arguments/Remarks Made in an Amendment	5	5

Warnings:					
Information:					
8	Oath or Declaration filed	20150703_Declaration.pdf	156712 c4516e8242fe813642c9e788924fe0cbb01639a9	no	2
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Information:					
9	Drawings-only black and white line drawings	20150803_Replacement_Drawings.pdf	232781 3758b55e524cbccad3058b4c0d977f854fdf05fc	no	3
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	40423 547c92e17d0b387901745ff99a4d9ae3eda78b1f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2772971		

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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.

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

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

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

Application Number	Filing Date

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

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

OR

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

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

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

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

Horizon Therapeutics, Inc.

☐ Inventor or Joint Inventor (title not required below)

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

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

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

SIGNATURE of Applicant for Patent

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

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

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

☐ Total of forms are submitted.

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

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

Electronic Acknowledgement Receipt	
EFS ID:	23099543
Application Number:	14816674
International Application Number:	
Confirmation Number:	9599
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Lauren Stevens/Vicki Truman
Filer Authorized By:	Lauren Stevens
Attorney Docket Number:	HOR0026-201-C1US
Receipt Date:	03-AUG-2015
Filing Date:	
Time Stamp:	16:42:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	Horizon_Therapeutics_Applicant.pdf	106357 f674dfc6ed140e4b2710f2e8e0c1dae0af853ed0	no	1
Warnings:					
Information:					

Total Files Size (in bytes):	106357

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/816,674	08/03/2015	1736	1600	HOR0026-201-C1US	3	1

CONFIRMATION NO. 9599

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

FILING RECEIPT

OC000000078936861

Date Mailed: 08/20/2015

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 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.

If Required, Foreign Filing License Granted: 08/18/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/816,674**

Projected Publication Date: 11/26/2015

Non-Publication Request: No

Early Publication Request: No

Title

METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

Preliminary Class

423

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

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NOT GRANTED

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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/816,674

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	3 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						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	1600

APPLICATION AS AMENDED - PART II

AMENDMENT A

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

AMENDMENT B

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/816,674	Filing Date 08/03/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

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

APPLICATION AS AMENDED – PART II

AMENDMENT	08/20/2015	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 3	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/BRENDA HINES/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/816,674	08/03/2015	Bruce Scharschmidt	HOR0026-201TC1-US	9599

101325 7590 08/27/2015

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

EXAMINER
RAO, SAVITHA M

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
08/27/2015	ELECTRONIC

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

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

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

Lstevens@globalpatentgroup.com
admin@globalpatentgroup.com
vtruman@globalpatentgroup.com

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Doc Code:
TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/816,674

1. THE REQUEST FILED August 03, 2015 IS **GRANTED.**

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

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

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

Telephone inquiries with regard to this decision should be directed to JoAnne Burke at 571-272-4584. In his/her absence, calls may be directed to Brian Brown, 571-272-5338.

/JoAnne Burke/
[*Signature*]

Paralegal Specialist, Office of Petitions
(Title)

Office of Petitions: Decision Count Sheet

Mailing Month

Application No. 14816674

14816674

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: BURKE, JOANNE

Count (1) - Palm Credit 14/816,674

Decision: GRANT

FINANCE WORK NEEDED ☐ Select Check Box for YES

GRANT

Decision Type: 643 - Track One request

643

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED ☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED ☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

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

Printed on:

Office of Petitions Internal Document - Ver. 5.0

Office of Petitions: Routing Sheet

Application No. 14/816,674

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

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/816,674	08/03/2015	Bruce Scharschmidt	HOR0026-201TC1-US	9599

101325 7590 11/03/2015

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

EXAMINER	
RAO, SAVITHA M	

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
11/03/2015	ELECTRONIC

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

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

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

Lstevens@globalpatentgroup.com
admin@globalpatentgroup.com
vtruman@globalpatentgroup.com

Office Action Summary	Application No. 14/816,674	Applicant(s) SCHARSCHMIDT ET AL.	
	Examiner SAVITHA RAO	Art Unit 1621	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *08/03/2015*.

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

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

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

Disposition of Claims*

5)☒ Claim(s) *12-14* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *21-14* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

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

DETAILED ACTION

Claims 12-14 are pending and are under consideration in the instant office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 08/03/2015 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 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 12-14 are rejected on the ground of nonstatutory double patenting over claim 3-6 of U. S. Patent No 8,404,215 (‘215) and claims1-15 of U.S. Patent No 9,095,559 (‘559) claims since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patents.

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

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

Instant claims are as follows:

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.

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

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

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 claims 13-14 are recited in the claims of parent patent '215. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are rendered prima facia obvious to a person of ordinary skill in the art to utilize the specific agent instantly claimed which is taught in claim 6 of '215 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-phenylburyrate] 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-phenylburyrate] 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 in claims 13-14 are recited in the claims of parent patent '559. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are rendered prima facia obvious to a person of ordinary skill in the art as they are both drawn to the same subject matter. It is also noted that the steps in following the instant method is the same as that claimed in '559.

Claim 12-14 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 12-14 recite as stated above

Claims 1of '012 recite as follows:

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

'012 recite a method for treating urea cycle in a subject by administering glyceryl-tri-(4-phenylbutyrate). The other limitations instantly claimed in claims 13-14 are recited in the claims of parent patent '012. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are rendered prima facia obvious to a person of ordinary skill in the art as they are both drawn to the same

subject matter. It is also noted that the steps in following the instant method is the same as that claimed in '012.

.

Conclusion

Claims 12-14 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.

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SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/816,674	08/03/2015 RULE	424	1621	HOR0026-201TC1-US

APPLICANTS
Horizon Therapeutics, Inc., Deerfield, IL;

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

**** CONTINUING DATA **************************
This application is a CON of 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

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Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
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Sheet 1 of 13

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First Named Inventor	Bruce Scharschmidt
Art Unit	TBA
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Attorney Docket Number	HOR0026-201C1-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication or Issue Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	P1	4,457,942	07-03-1984	Brusilow, S.W.	
	P2	5,654,333	08-05-1997	The United States Of America As Represented By The Department Of Health And Human Services	
	P3	8,094,521	01-10-2012	Nightengale Products LLC	
	P4	8,404,215	03-26-2013	Hyperion Therapeutics, Inc.	
	P5	2003/0195255	10-16-2003	Marshall L. Summar	
	P6	2005/0273359	12-08-2005	Young, D.E.	
	P7	2010/0016207	01-21-2010	Wurtman, RJ et al	
	P8	2013/0281530	10-24-2013	Scharschmidt, B et al	
	P9	2014/0142186	05-22-2014	Hyperion Therapeutics, Inc.	
	P10	6,219,567	4/17/2001	EGGERS	
	P11	8,642,012	2/4/2014	SCHARSCHMIDT	
	P12	2010/0008859	1/14/2010	SCHARSCHMIDT	
	P13	2012/0022157	1/26/2012	SCHARSCHMIDT	
	P14	9,078,865	7/14/2015	LEE	
	P15	2013/0210914	8/15/2013	SCHARSCHMIDT	
	P16	2008/0119554	5/22/2008	JALAN	

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	F2	WO2013/048558	04-04-2013	Hyperion Therapeutics, Inc.		
	F3	WO2013/158145	10-24-2013	Hyperion Therapeutics, Inc.		
	F4	WO2007/005633				
	F5	WO2009/087474	7/16/2009	Akthelia Pharmaceuticals		
	F6	WO2012/028620				

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Sheet 3 of 13

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Sheet 4 of 13

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First Named Inventor	Bruce Scharschmidt
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First Named Inventor	Bruce Scharschmidt
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	D43	International Search Report and Written Opinion for PCT/US09/30362, mailed Mar. 2, 2009, 8 pages.	
	D44	International Search Report and Written Opinion for PCT/US2009/055256, mailed Dec. 30, 2009, 13 pages.	
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First Named Inventor	Bruce Scharschmidt
Art Unit	TBA
Examiner Name	TBA
Attorney Docket Number	HOR0026-201C1-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
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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
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S18	9	((Saul) near2 (Brusilow)).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; EPO;	OR	OFF	2012/12/20 10:56

		| "6219567").PN.	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

EAST Search History (Interference)

<This search history is empty>

10/ 29/ 2015 10:40:47 AM
H:\ EAST - WKSP\ Workspaces\ 14 applications\ 14816674.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14816674	SCHARSCHMIDT ET AL.
	Examiner	Art Unit
	SAVITHA RAO	1621

CPC- SEARCHED		
Symbol	Date	Examiner
A61K31/216 OR G01N31/221 OR Y10T436/175383	5/14/2015	SR

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	9.2	10/29/2015	SR
514	432, 433, 544, 570, 533	10/29/2015	SR
436	4,113	10/29/2015	SR

SEARCH NOTES		
Search Notes	Date	Examiner
eaST search (See attached)	10/29/2015	SR
Inventor search in EAST and PALM	10/29/2015	SR
Reviewed STN searches from the Parent application, further NPL search in Google	10/29/2015	SR

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/216	10/29/2015	SR
G01N	31/221	10/29/2015	SR
Y10T	436/175383	10/29/2015	SR
424	9.2	10/29/2015	SR
514	533, 432, 433, 544, 570	10/29/2015	SR
435	4, 113	10/29/2015	SR

	/SAVITHA RAO/ Primary Examiner.Art Unit 1621

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Title:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
Application. No.:	14/816,674
Filing Date:	August 3, 2015
Examiner:	Savitha M. Rao
Art Unit:	1621
Confirmation Number:	9599

RESPONSE

ELECTRONICALLY VIA EFS-WEB

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

Sir:

Applicant responds to the Office action mailed November 3, 2015. Claims 12-14 are pending.

The claims are rejected on the ground of nonstatutory double patenting over claims 3-6 of U.S. Patent No. 8,404,215 and claims 1-15 of U.S. Patent No. 9,095,559. The claims are also rejected on the ground of nonstatutory double patenting over claims 3-6 of U.S. Patent No. 8,642,012. Solely to expedite prosecution and without in any way conceding to the rejections, Applicant submits herewith terminal disclaimers over those patents. Applicant requests that the rejection be withdrawn.

Applicant believes that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested. If new issues of patentability are raised, the Examiner is invited to call or email the undersigned and arrange for an opportunity to discuss these issues.

Respectfully submitted,

By /Lauren L. STEVENS/

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

Atty Docket No.: HOR0026-201TC1-US

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Scharschmidt et al.	)
			) Group Art Unit:
Serial No.	:	14/816,674	) 1621
			)
Filed	:	August 3, 2015	)
			) Examiner:
			) Rao, Savitha M.

Title: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

NOTICE OF RELATED LITIGATION

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

Further to the Notice of Related Litigation filed August 3, 2015, 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, Lupin Ltd. ("Lupin") sent a PIV notice letter to Horizon Therapeutics, Inc. ("Horizon") on Sept. 4, 2015 providing notice that Lupin had filed an Abbreviated New Drug Application ("ANDA") with respect to RAVICTI® (Glycerol Phenylbutyrate) Oral Liquid, with a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") alleging that U.S. Patent Nos. 8,404,215 and 8,642,012 are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the Lupin drug product.

Under 21 U.S.C. § 355(j)(5)(B)(iii), Horizon had forty-five days from receipt of the ANDA notice letter to file suit against Lupin for patent infringement. Accordingly, on October 19, 2015, Horizon brought suit on those patents against Lupin Ltd. And Lupin Pharmaceuticals, Inc. in the United States District Court for the District of New Jersey. The Complaint alleged that Lupin infringes U.S. Patent Nos. 8,404,215 and 8,642,012. The subject application is a

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

Respectfully submitted,

By /Lauren L. STEVENS/

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

Attorney Docket No.: HOR0026-201C1-US

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Scharschmidt et al.	)
			) Group Art Unit:
Serial No.	:	14/816,674	) 1621
			)
Filed	:	8/03/2015	)
			) Examiner:
			) Rao, Savitha M.

Title: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.561

ELECTRONICALLY VIA EFS-WEB

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

Sir:

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

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

Applicant requests that, in accordance with 37 CFR §1.98(d), the Examiner review all applications relied on for an earlier effective filing date under 35 U.S.C. 120, including application no. 13/775,000, filed February 22, 2013, now U.S. Patent No. 9,095,559, and application no. 13/417,137, filed March 9, 2012, now U.S. Patent 8,404,215, for copies of

references of record therein that are not being provided here; although Applicant would be pleased to provide copies of any such documents at the Examiner's request.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

The Commissioner is hereby authorized to charge any fees which may be due to Deposit Account No. 50-4297.

Respectfully submitted,

By /Lauren L. STEVENS/

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

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

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 10

Complete if Known	
Application Number	14/816674
Filing Date	8/03/2015
First Named Inventor	Bruce Scharschmidt
Art Unit	1621
Examiner Name	Rao, Savitha M.
Attorney Docket Number	HOR0026-201TC1-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication or Issue Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	P1	2004/0229948	11/18/2004	SUMMAR et al.	
	P2	2006/0135612	06/22/2006	FERRANTE	
	P3	2012/0220661	08/30/2012	LEE	
	P4	4,284,647	08/18/1981	BRUSILOW et al.	
	P5	5,968,979	10/19/1999	BRUSILOW	
	P6	6,060,510	05/09/2000	BONNEWITZ	
	P7	6,083,984	07/04/2000	BRUSILOW	
	P8	2015/0094278	03/26/2015	SCHARSCHMIDT et al.	
	P9	2015/0105469	04/16/2015	SCHARSCHMIDT et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	F1	WO2005/053607	06/16/2005	MEDICIS PHARMACEUTICAL CORP.		
	F2	WO2006/056794	06/01/2006	UCL BUSINESS PLC		
	F3	WO2009/134460	11/05/2009	HYPERION THERAPEUTICS		
	F4	WO2010/025303	03/04/2010	HYPERION THERAPEUTICS		

Examiner Signature		Date Considered	

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

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

Substitute for form 1449/PTO				***Complete if Known***	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/816674
				Filing Date	8/03/2015
				First Named Inventor	Bruce Scharschmidt
				Art Unit	1621
(use as many sheets as necessary)				**Examiner Name**	Rao, Savitha M.
Sheet	2	of	10	**Attorney Docket Number**	HOR0026-201TC1-US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue BUSINESS number(s), publisher, city and/or country where published.	T[6]
	D1	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	
	D2	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.	
	D3	AMBROSE, A.M. et al. (1933). "Further Studies on the Detoxification of Phenylacetic Acid," J. Bio. Chem. 101:669-675.	
	D4	BATSHAW, M.L. et al. (December 1980). "Treatment of Hyperammonemic Coma Caused by Inborn Errors of Urea Synthesis," J. Pediatr. 97(6):893-900.	
	D5	BATSHAW M.L. et al. (June 10, 1982). "Treatment of Inborn Errors of Urea Synthesis: Activation of Alternative Pathways of Waste Nitrogen Synthesis and Excretion," N. Engl. J. Med. 306(23):1387-1392.	
	D6	BATSHAW, M.L. (1984). "Hyperammonemia," in Current Problems in Pediatrics, Lockhart, J.D. ed.: Year Book Medical Publishers, pp. 2-69.	
	D7	BERRY, G. T., et al., "Long-Term Management of Patients with Urea Cycle Disorders," J. Pediatrics (2001) 138:S56-S61.	
	D8	BRUSILOW, S., et al., "Amino Acid Acylation: A Mechanism of Nitrogen Excretion in Inborn Errors of Urea Synthesis," Science 207:659-661 (1980).	
	D9	BRUSILOW, S. W., et al., "Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion," Pediatr. Res. 29:147-150 (1991).	
	D10	BRUSILOW, S.W. et al. (September 1,1979). "New Pathways of Nitrogen Excretion in Inborn Errors of Urea Synthesis," Lancet 2(8140):452- 454.	
	D11	BRUSILOW, S.W. (June 21,1984). "Treatment of Episodic Hyperammonemia in Children With Inborn Errors of Urea Synthesis," N. Engl. J. Med. 310(25):1630- 1634.	

Examiner Signature		Date Considered	

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 3 of 10

Complete if Known	
Application Number	14/816674
Filing Date	8/03/2015
First Named Inventor	Bruce Scharschmidt
Art Unit	1621
Examiner Name	Rao, Savitha M.
Attorney Docket Number	HOR0026-201TC1-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue BUSINESS number(s), publisher, city and/or country where published.	T[6]
	D12	BRUSILOW, S.W. (Amendment Dated July 25, 1994). "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.	
	D13	BRUSILOW, S.. et al. (1991). "Treatment of Urea Cycle Disorders," Chapter 5 *in* Treatment of Genetic Diseases, Desnik, R.J. et al. eds, Churchill Livingstone, New York, New York, pp. 79-94.	
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	D15	BRUSILOW, S.W., et al. (1996)." Urea Cycle Disorders: Diagnosis, Pathophysiology, and Therapy," Adv. Pediatr. 43:127-170.	
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	D21	CHANG J.-G., et al., "Treatment of Spinal Muscular Atrophy by Sodium Butyrate," PNAS USA (2001) 98(17):9808-9813.	
	D22	ClinicalTrials.Gov/Archive View of NCT00551200 on 2007 12 11 "Dose- Escalation Safety Study of Glyceryl Tri (4-Phenylbutyrate)(GT4P) to Treat Urea Cycle Disorders" [accessed 5 October 2009], 4 pages.	

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Application Number	14/816674
Filing Date	8/03/2015
First Named Inventor	Bruce Scharschmidt
Art Unit	1621
Examiner Name	Rao, Savitha M.
Attorney Docket Number	HOR0026-201TC1-US

NON PATENT LITERATURE DOCUMENTS

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	D23	Combined Search and Examination Report mailed on September 9, 2010, for Great Britain Patent Application No. 1013468.2, filed on August 27, 2009, six pages.	
	D24	Combined Search and Examination Report mailed on October 9, 2009, for Great Britain Patent Application No. GB0915545.8, filed on August 27, 2009, eight pages.	
	D25	'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.	
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	D29	DEFERRARI, G. et al. (1981). "Brain Metabolism of Amino Acids and Ammonia in Patients with Chronic Renal Insufficiency," Kidney International 20:505-510.	
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	D34	Examination Report mailed May 11, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on August 27,2009, one page.	

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				Filing Date	8/03/2015
				First Named Inventor	Bruce Scharschmidt
				Art Unit	1621
				Examiner Name	Rao, Savitha M.
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	D36	FDA. (August 2003). "Buphenyl® (Sodium Phenylbutyrate) Label" nine pages.	
	D37	FDA Label for BUPHENYL, 6 pages.	
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	D43	GROPMAN, A.L., et al., "1**H** MRS Identifies Symptomatic and Asymptomatic Subjects with Partial Ornithine Transcarbamylase Deficiency," Mol. Genet. Metab. 95:21-30 (2008).	
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				Art Unit	1621
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	D45	HYPERION THERAPEUTICS. (June 2, 2009.) "Hyperion Therapeutics Announces Results of Phase I Study in Patients with Liver Cirrhosis" located at<http://www.hyperiontx.com/press/release/pr 1243891161>, last visited on April 27, 2011, three pages.	
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	D54	LEE, B. et al. (August 2009). "Dosing and Therapeutic Monitoring of Ammona Scavenging Drugs and Urinary Phenylacetylglutamine (PAGN) as a Biomarker: Lessons From a Phase 2 Comparison of a Novel Ammonia Scavenging Agent with Sodium Phenyl butyrate (NAPBA)," presented at ICIEM 2009, San Diego, CA, poster, one page.	

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	D55	LEE, B. et al. (March 2009). "Phase 2 Study of A Novel Ammonia Scavenging Agent in Adults With Urea Cycle Disorders (UCDs)," abstract presented at ACMG 2009, one page.	
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	D61	LEWIS, H.B. (1914). "Studies in the Synthesis of Hippuric Acid in the Animal Organism. II. The Synthesis and Rate of Elimination of Hippuric Acid After Benzoate Ingestion In Man," J. Bioi. Chem. 18 :225-231.	
	D62	LEVIN, B. et al. "Hyperammonaemia: A Variant Type of Deficiency of Ornithinine Transcarbamylase." Arch. Dis. Childhd. 1969, 44, 162-169.	
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	D65	MANSOUR, A. et al. (October 1997). "Abdominal Operations in Patients with Cirrhosis: Still A Major Surgical Challenge," Surqerv 122(4):730-735. (Abstract Only.)	
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	D73	PISCITELLI, S.C. et al. (1995). "Disposition of Phenyl butyrate and its Metabolites, Phenylacetete and Phenylacetylglutamine," J. Clin. Pharmacal. 35:368-373.	

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	D81	SUMMAR, M.L. et al. (October 2008, e-pub. July 17, 2008). "Diagnosis, Symptoms, Frequency and Mortality of 260 Patients with Urea Cycle Disorders From a 21-Year, Multicentre Study of Acute Hyperammonaemic Episodes," Acta Paediatr. 97:1420-1425.	
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	D85	THIBAULT, A., et al., "A Phase I and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer," Cancer Res. 54:1690-1694 (1994).	
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	D91	ZEITLIN, P.L. et al. (July 2002). "Evidence of CFTR Function in Cystic Fibrosis After System Administration of 4-Phenylbutyrate," Mol. Therapy 6(1):119-126.	

Examiner Signature		Date Considered	

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

Electronic Patent Application Fee Transmittal

Application Number:	14816674
Filing Date:	03-Aug-2015
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Lauren Stevens/Vicki Truman
Attorney Docket Number:	HOR0026-201TC1-US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	23998454
Application Number:	14816674
International Application Number:	
Confirmation Number:	9599
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Lauren Stevens/Vicki Truman
Filer Authorized By:	Lauren Stevens
Attorney Docket Number:	HOR0026-201TC1-US
Receipt Date:	05-NOV-2015
Filing Date:	03-AUG-2015
Time Stamp:	17:08:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	4034
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	Amendment/Req. Reconsideration-After Non-Final Reject	20151105_Response.pdf	17114 363c62eb0f470f9a9103f46a04d5bd9f861f590e	no	2
Warnings:					
Information:					
2	Notice of concurrent proceedings / decisions	20151105_NRL.pdf	18751 d840afcf1cf8545b386acf9a70d2718747740a11	no	2
Warnings:					
Information:					
3	Transmittal Letter	20151105_IDS_Trans.pdf	21725 bc4ed1d6d68beaf3ca10785484d0fd98c6bb8234	no	2
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	20151105_IDS.pdf	152671 e903bb3d413810ef6d4dbd20003ee17d2d8f53fb	no	10
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
5	Non Patent Literature	Lupin_Ravicti_ANDA_Notice9142015.pdf	3027128 e5bf5dc9c76c63b0ff7317b505e7c14a07d7da16	no	57
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6	Non Patent Literature	Levin_1969.pdf	1122759 d6494cf8e99fec1667781a156567626179ccdc08	no	8
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7	Non Patent Literature	Complaint_HorizonvLupin_Ravicti10192015.pdf	14821002 07ae20afee7b3f3967e3da62b11b36d66a21f323	no	104
Warnings:					
Information:					

8	Non Patent Literature	Lab_Updates.pdf	228668 ebe300d7ba9fcc1f66f3e8fe723df4dd71e1a445	no	3
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Information:					
9	Non Patent Literature	Aherns_2001.PDF	303549 0deaf51a0d56849361f6fe7f5f08e013eee0d4d7	no	5
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10	Non Patent Literature	DarzensG_1937.pdf	89679 08521d007b0a9165826724457e994edd86e1f983	no	3
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Information:					
11	Non Patent Literature	Diaz_2011.PDF	168683 21d1de3dcae3b6a51cf84586bc0e7b79ab521bdc	no	1
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12	Non Patent Literature	FDA_Label_2005.pdf	256698 735fe8649f8d8481ae3ccc5e839263411814c74e	no	16
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Information:					
13	Non Patent Literature	LeaMA_etal_AnticancerRes_1993.pdf	454953 d4436f67441cea41a904be0b8085a676ecc2954d	no	6
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
14	Non Patent Literature	Seiki.pdf	34237 787645771bfbbb0cf5f8c05135533f309e1a9bc6	no	1
Warnings:					
Information:					
15	Non Patent Literature	Walsh_1990.pdf	2442362 44f00667e82972c48d8d7ab7b390cce83dd1c77f	no	9
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16	Non Patent Literature	20140423_Complaint_Hyperion1.pdf	162818 d5891349c03acd89041788ccbaccecdcfd548655	no	14

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Information:					
17	Fee Worksheet (SB06)	fee-info.pdf	30674 6077626cda5f218e2169f11416f9d9797171871e	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	23353471	

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

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

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	14816674
Filing Date	03-Aug-2015
First Named Inventor	Bruce Scharschmidt
Attorney Docket Number	HOR0026-201TC1-US
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

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

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

Owner	Percent Interest
Horizon Therapeutics, Inc.	100%
Horizon Therapeutics, Inc.	100%
Horizon Therapeutics, Inc.	100%

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

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9095559

8642012

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 36691

○ 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	/Lauren Stevens/
Name	Lauren Stevens

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

Electronic Patent Application Fee Transmittal

Application Number:	14816674
Filing Date:	03-Aug-2015
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Lauren Stevens/Vicki Truman
Attorney Docket Number:	HOR0026-201TC1-US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Statutory or Terminal Disclaimer	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

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

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

Application No.: 14816674

Filing Date: 03-Aug-2015

Applicant/Patent under Reexamination: Scharschmidt et al.

Electronic Terminal Disclaimer filed on November 5, 2015

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

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

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt	
EFS ID:	24002742
Application Number:	14816674
International Application Number:	
Confirmation Number:	9599
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Lauren Stevens/Vicki Truman
Filer Authorized By:	Lauren Stevens
Attorney Docket Number:	HOR0026-201TC1-US
Receipt Date:	05-NOV-2015
Filing Date:	03-AUG-2015
Time Stamp:	17:27:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	4320
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	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	36096 5b4ae1589fc1318399f70e9c8b9d605cfa0bc9a9	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30482 c384922573637ba966dccefdf271b2dc85d13ec0	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	66578		

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

Electronic Acknowledgement Receipt

EFS ID:	24003296
Application Number:	14816674
International Application Number:	
Confirmation Number:	9599
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Dennis A. Bennett/Ronnie Almira
Filer Authorized By:	Dennis A. Bennett
Attorney Docket Number:	HOR0026-201TC1-US
Receipt Date:	05-NOV-2015
Filing Date:	03-AUG-2015
Time Stamp:	17:57:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	MOKHTARANI_etal_2012_Abstract78.pdf	59499 4ea4eb29a1a2b0cb26e046ed2b828d3e53d9d0ab	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	59499

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

New Applications Under 35 U.S.C. 111
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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.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Title:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
Application. No.:	14/816,674
Filing Date:	August 3, 2015
Examiner:	Savitha M. Rao
Art Unit:	1621
Confirmation Number:	9599

AMENDMENT

ELECTRONICALLY VIA EFS-WEB

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

Sir:

Applicant respectfully requests that the application be amended as follows:

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

Remarks/Arguments begin following the Amendments to the Claims.

Amendments to the Claims

This listing of claims replaces all prior versions, and listings, of claims in the present application.

1.-11. (Cancelled)

12. (Previously Presented) 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.

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

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

15. (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 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, and

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

16. (New) The method of claim 15, 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.

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

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

19. (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 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, and

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.

20. (New) The method of claim 19, 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.

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

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

23. (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 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;

(c) 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

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

24. (New) The method of claim 23, 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.

25. (New) The method of claim 23, wherein the initial dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

26. (New) The method of claim 23, wherein the adjusted dosage of glyceryl tri-[4-phenylbutyrate] is administered orally.

Remarks

Claims 15-26 have been added. Support for this amendment can be found, e.g., in the specification as filed at [0005], [0007], [0069], [0079], [0082], [0083], and [0085]. See, also, the issued claims of U.S. Patent No. 9,095,559, which is the parent of the subject application. With entry of this amendment, claims 12-26 are pending.

Applicant believes that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested. If new issues of patentability are raised, the Examiner is invited to call or email the undersigned and arrange for an opportunity to discuss these issues.

Respectfully submitted,

By /Lauren L. STEVENS/

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

Electronic Patent Application Fee Transmittal

Application Number:	14816674
Filing Date:	03-Aug-2015
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Lauren Stevens/Vicki Truman
Attorney Docket Number:	HOR0026-201TC1-US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

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

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

Electronic Acknowledgement Receipt	
EFS ID:	24149163
Application Number:	14816674
International Application Number:	
Confirmation Number:	9599
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Lauren Stevens/Vicki Truman
Filer Authorized By:	Lauren Stevens
Attorney Docket Number:	HOR0026-201TC1-US
Receipt Date:	20-NOV-2015
Filing Date:	03-AUG-2015
Time Stamp:	15:38:16
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$420
RAM confirmation Number	2270
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		20151120_Response.pdf	34993 07dd3f7efcf6729fa9fe8bb3a03b4c1c78339312	yes	5

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	5

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30755 59e77b7953f61fca1b8d93e6b7d6353ce34fdad5	no	2

Warnings:

Information:

Total Files Size (in bytes):	65748

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

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

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/816,674	Filing Date 08/03/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

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

APPLICATION AS AMENDED – PART II

AMENDMENT **11/20/2015**

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

AMENDMENT

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

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

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

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

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

LIE
/DORIS BURNS/

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/816,674	08/03/2015	Bruce Scharschmidt	HOR0026-201TC1-US

CONFIRMATION NO. 9599

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

PUBLICATION NOTICE

OC000000078919748

Title:METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

Publication No.US-2015-0335605-A1
Publication Date:11/26/2015

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

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
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NOTICE OF ALLOWANCE AND FEE(S) DUE

101325 7590 12/23/2015

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: 12/23/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/816,674	08/03/2015	Bruce Scharschmidt	HOR0026-201TC1-US	9599

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	03/23/2016

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 12/23/2015
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.
14/816,674	08/03/2015	Bruce Scharschmidt	HOR0026-201TC1-US	9599

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	03/23/2016

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

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

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

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

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

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

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

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

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

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

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/816,674	08/03/2015	Bruce Scharschmidt	HOR0026-201TC1-US	9599

101325 7590 12/23/2015

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: 12/23/2015

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

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

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

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

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

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

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

Privacy Act Statement

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

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

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

Notice of Allowability	Application No. 14/816,674	Applicant(s) SCHARSCHMIDT ET AL.	
	Examiner SAVITHA RAO	Art Unit 1621	AIA (First Inventor to File) Status No

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

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

1. ☒ This communication is responsive to *11/20/2015*.
   ☐ 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 *13-26*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

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

   * Certified copies not received: _____.

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

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

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

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 11/05/2015
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SAVITHA RAO/
Primary Examiner, Art Unit 1621

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

DETAILED ACTION

Claims 12-26 are pending in the instant application.

Applicants present new claims 15-26 with their response on 11/05/2015.

The terminal disclaimer filed on 11/05/2015 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US patent nos. 8,404,215, 9,095,559 and 8,642,012 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Information Disclosure Statement

The information disclosure statement (IDS) dated 11/05/2015 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.

REASONS FOR ALLOWANCE

In view of the applicants arguments filed on 11/20/2015 and terminal disclaimer filed on 11/05/2015 and the following examiners statement of reasons for allowance, claims 12-26 are found to be allowable. Upon further review, new claims 15-26 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 15-26 are also found to be allowable along with originally presented claims 12-14.

Following a diligent search it was determined that the prior art neither teaches nor provides adequate motivation to arrive at the instantly claimed 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 and 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, and

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

or

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.

Conclusion

Claims 12-26 (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.

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/SAVITHA RAO/

Primary Examiner, Art Unit 1621

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14816674	SCHARSCHMIDT ET AL.
	Examiner	Art Unit
	SAVITHA RAO	1621

CPC- SEARCHED		
Symbol	Date	Examiner
A61K31/216 OR G01N31/221 OR Y10T436/175383	12/15/2015	SR

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	9.2	10/29/2015	SR
514	432, 433, 544, 570, 533	10/29/2015	SR
436	4,113	10/29/2015	SR

SEARCH NOTES		
Search Notes	Date	Examiner
eaST search (See attached)	10/29/2015	SR
Inventor search in EAST and PALM	10/29/2015	SR
Reviewed STN searches from the Parent application, further NPL search in Google	10/29/2015	SR
updated EAST search (see attached)	12/15/2015	SR
updated inventor search in EAST	12/15/2015	SR
Reviewed STN searches and NPL search in Google	12/15/2015	

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/216	12/15/2015	SR
G01N	31/221	12/15/2015	SR
Y10T	436/175383	12/15/2015	SR

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Sheet 1 of 10

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Application Number	14/816674
Filing Date	8/03/2015
First Named Inventor	Bruce Scharschmidt
Art Unit	1621
Examiner Name	Rao, Savitha M.
Attorney Docket Number	HOR0026-201TC1-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication or Issue Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	P1	2004/0229948	11/18/2004	SUMMAR et al.	
	P2	2006/0135612	06/22/2006	FERRANTE	
	P3	2012/0220661	08/30/2012	LEE	
	P4	4,284,647	08/18/1981	BRUSILOW et al.	
	P5	5,968,979	10/19/1999	BRUSILOW	
	P6	6,060,510	05/09/2000	BONNEWITZ	
	P7	6,083,984	07/04/2000	BRUSILOW	
	P8	2015/0094278	03/26/2015	SCHARSCHMIDT et al.	
	P9	2015/0105469	04/16/2015	SCHARSCHMIDT et al.	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	F1	WO2005/053607	06/16/2005	MEDICIS PHARMACEUTICAL CORP.		
	F2	WO2006/056794	06/01/2006	UCL BUSINESS PLC		
	F3	WO2009/134460	11/05/2009	HYPERION THERAPEUTICS		
	F4	WO2010/025303	03/04/2010	HYPERION THERAPEUTICS		

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	D1	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	
	D2	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.	
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	D6	BATSHAW, M.L. (1984). "Hyperammonemia," in Current Problems in Pediatrics, Lockhart, J.D. ed.: Year Book Medical Publishers, pp. 2-69.	
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	D9	BRUSILOW, S. W., et al., "Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion," Pediatr. Res. 29:147-150 (1991).	
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Attorney Docket Number	HOR0026-201TC1-US

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	D12	BRUSILOW, S.W. (Amendment Dated July 25, 1994). "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.	
	D13	BRUSILOW, S.. et al. (1991). "Treatment of Urea Cycle Disorders," Chapter 5 *in* Treatment of Genetic Diseases, Desnik, R.J. et al. eds, Churchill Livingstone, New York, New York, pp. 79-94.	
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	D21	CHANG J.-G., et al., "Treatment of Spinal Muscular Atrophy by Sodium Butyrate," PNAS USA (2001) 98(17):9808-9813.	
	D22	ClinicalTrials.Gov/Archive View of NCT00551200 on 2007 12 11 "Dose- Escalation Safety Study of Glyceryl Tri (4-Phenylbutyrate)(GT4P) to Treat Urea Cycle Disorders" [accessed 5 October 2009], 4 pages.	

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Sheet 4 of 10

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Application Number	14/816674
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First Named Inventor	Bruce Scharschmidt
Art Unit	1621
Examiner Name	Rao, Savitha M.
Attorney Docket Number	HOR0026-201TC1-US

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	D23	Combined Search and Examination Report mailed on September 9, 2010, for Great Britain Patent Application No. 1013468.2, filed on August 27, 2009, six pages.	
	D24	Combined Search and Examination Report mailed on October 9, 2009, for Great Britain Patent Application No. GB0915545.8, filed on August 27, 2009, eight pages.	
	D25	'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.	
	D26	'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.	
	D27	COMTE, B., et al., "Identification of Phenylbutyrylglutamine, A new Metabolite of Phenylbutyrate Metabolism in Humans," Journal of Mass Spectrometry (2002) 37(6):581-590.	
	D28	DARZENS, G. et al.: "Preparation de quelques glycerides phenylaliphatiques et leur reduction en alcools ... ", COMPTES RENDUS HEBDOMADAIRES DES SEANCES DE L'ACADEMIE DES SCIENCES., vol. 205, 18 October 1937, pgs. 682-684.	
	D29	DEFERRARI, G. et al. (1981). "Brain Metabolism of Amino Acids and Ammonia in Patients with Chronic Renal Insufficiency," Kidney International 20:505-510.	
	D30	DIAZ, G.A., et al., "Phase 3 Blinded, Randomized, Crossover Comparison of Sodium Phenylbutyrate (NaPBA) and Glycerol Phenylbutyrate (GPB): Ammonia (NH3) Control in Adults with Urea Cycle Disorders (UCDs)," Mol. Genet. Metab. 102:276 (2011).	
	D31	DIAZ G.A.et al, "Ammonia (NH3) control and improved neurocognitive outcome among urea cycle disorder (UCD) patients treated with glycerol phenylbutyrate (GPB)." Mol. Genet. Metab. 2012, 105, 311, SIMD Abstract 24.	
	D32	Examination Report mailed on October 27, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on August 27,2009, two pages.	
	D33	Examination Report mailed February 5, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on August 27,2009, two page.	
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Sheet 5 of 10

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Application Number	14/816674
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	D35	FDA Label for Ammonul®, sixteen pages (Feb. 2005).	
	D36	FDA. (August 2003). "Buphenyl® (Sodium Phenylbutyrate) Label" nine pages.	
	D37	FDA Label for BUPHENYL, 6 pages.	
	D38	GARGOSKY, S. (2006). "High Ammonia Levels Are Associated With Increased Mortality and Coma," Ucyclyd Pharma, Inc., one page.	
	D39	GARGOSKY, S. et al. (October 14, 2005). "Results of a Twenty-two Year Clinical Trial: Actue, Adjunctive Pharmacological Treatment of Hyperammonemic Episodes in Patients with Deficiencies in Enzymes of the Urea Cycle," poster, Ucyclyd Pharma, Inc., one page.	
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	D42	GROPMAN, A. L., et al., "1**H** MRS Allows Brain Phenotype Differentiation in Sisters with Late Onset Ornithine Transcarbamylase Deficiency (OTCD) and Discordant Clinical Presentations," Mol. Genet. Metab. 94(1):52-60 (2008).	
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	D45	HYPERION THERAPEUTICS. (June 2, 2009.) "Hyperion Therapeutics Announces Results of Phase I Study in Patients with Liver Cirrhosis" located at<http://www.hyperiontx.com/press/release/pr 1243891161>, last visited on April 27, 2011, three pages.	
	D46	International Preliminary Report on Patentability mailed on March 1, 2011, for PCT Application No. PCT/US2009/030362, filed on January 7, 2009, seven pages.	
	D47	International Preliminary Report on Patentability mailed on March 1, 2011, for PCT Application No. PCT/US2009/055256, filed on August 27, 2009, six pages.	
	D48	JAMES, M.O. et al. (1972). "The Conjugation of Phenylacetic Acid in Man, Sub- Human Primates and Some Other Non-Primates Species," Proc. R. Soc. London 182:25-35.	
	D49	JOHN, B.A. et al. (March 2009). "The Disposition of HPN-100, A Novel Pharmaceutical Under Development for Potential Treatment of Hyperammonemia, in Cynomologus Monkeys," abstract presented at ACMG 2009, one page.	
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	D52	LEA et al., "Butyramide and Monobutyrin: Growth Inhibitory and Differentiating Agents", ANTICANCER RES., 13: 145-150 (1993).	
	D53	LEE, B. et al. (August 2009). "Dosing and Therapeutic Monitoring of Ammonia Scavenging Drugs and Urinary Phenylacetylglutamine (PAGN) as a Biomarker; Lessons From a Phase 2 Comparison of A Novel Ammonia Scavenging Agent With Sodium Phenylbutyrate (NaPBA),".abstract presented at ICIEM 2009, San Diego, CA, one page.	
	D54	LEE, B. et al. (August 2009). "Dosing and Therapeutic Monitoring of Ammona Scavenging Drugs and Urinary Phenylacetylglutamine (PAGN) as a Biomarker: Lessons From a Phase 2 Comparison of a Novel Ammonia Scavenging Agent with Sodium Phenyl butyrate (NAPBA)," presented at ICIEM 2009, San Diego, CA, poster, one page.	

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	D56	LEE, B. et al. (March 2009). "Phase 2 Study of A Novel Ammonia Scavenging Agent in Adults with Urea Cycle Disorders (UCDs)," presented at ACMG 2009, seventeen pages.	
	D57	LEE, B. et al. (August 2008). "Preliminary Data on Adult Patients with Urea Cycle Disorders (UCO) in an Open-Label, Switch-Over, Dose-Escalation Study Comparing a New Ammonia Scavenger, Glyceryl Tri (4-Phenylbutyrate) [HPN - 100], to Buphenyl® (Sodium Phenylbutyrate [PBA])," abstract presented at SSIEM 2008, Lisbon, Portugal, one page.	
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	D60	LEE, B., et al., "Preliminary Data on Adult Patients with Urea Cycle Disorders (UCO) in an Open-Label, Switch-Over, Dose-Escalation Study Comparing a New Ammonia Scavenger, Glyceryl Tri(4-Phenylbutyrate) (HPN-100), to Buphenyl (Sodium Phenylbutyrate (PBA))," J. Inherit. Metab. Dis. 31(Suppl. 1):91 (2008).	
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	D63	LIANG, K.Y., et al., "Longitudinal Data Analysis Using Generalized Linear Models," Biometrika 73(1):13-22 (1986).	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 8 of 10

Complete if Known	
Application Number	14/816674
Filing Date	8/03/2015
First Named Inventor	Bruce Scharschmidt
Art Unit	1621
Examiner Name	Rao, Savitha M.
Attorney Docket Number	HOR0026-201TC1-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue BUSINESS number(s), publisher, city and/or country where published.	T[6]
	D64	MACARTHUR, R. B., et al., "Pharmacokinetics of Sodium Phenylacetate and Sodium Benzoate Following Intravenous Administration as Both a Bolus and Continuous Infusion to Healthy Adult Volunteers," Mol. Genet. Metab. 81:S67-S73 (2004).	
	D65	MANSOUR, A. et al. (October 1997). "Abdominal Operations in Patients with Cirrhosis: Still A Major Surgical Challenge," Surqerv 122(4):730-735. (Abstract Only.)	
	D66	MASETRI, N.E. et al. (August 1992). "Plasma Glutamine Concentration: A Guide in the Management of Urea Cycle Disorders," J. Pediatr. 121 (2):259-261.	
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	D71	MCQUADE P.S. (1984). "Analysis and the Effects of Some Drugs on the Metabolism of Phenylethylamine and Phenylacetic Acid," Neuropsychopharmacol. Bioi. Psychiat. 8:607-614.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 9 of 10

Complete if Known	
Application Number	14/816674
Filing Date	8/03/2015
First Named Inventor	Bruce Scharschmidt
Art Unit	1621
Examiner Name	Rao, Savitha M.
Attorney Docket Number	HOR0026-201TC1-US

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	D74	PROPST, A. et al. (August 1995). "Prognosis and Life Expectancy in Chronic Liver Disease," Dig Dis Sci 40(8):1805-1815. (Abstract Only).	
	D75	RILEY, T.R. et al. (November 15, 2001). "Preventive Strategies in Chronic Liver Disease: Part II. Cirrhosos," Am. Fam. Physician 64(10):1735-1740. (Abstract Only).	
	D76	RUDMAN, D., et al., "Maximal Rates of Excretion and Synthesis of Urea in Normal and Cirrhotic Subjects," J. Clin. Invest. (1973) 52:2241-2249.	
	D77	SEIKI et al., "Homogenous Pharmaceutical Emulsions Containing Nonsteriodal Analogesics and Inflammation Inhibitors"Chemical Abstract, Vol. 116, No. 46308.	
	D78	SHIPLE, G.J. et al. (1922). "Synthesis of Amino Acids in Animal Organisms. I. Synthesis of Glycocoll and Glutamine in the Human Organism," J. Am. Chem. Soc. 44:618-624.	
	D79	SIMELL, 0., et al., "Waste Nitrogen Excretion Via Amino Acid Acylation: Benzoate and Phenylacetate in Lysinuric Protein Intolerance," Pediatr. Res. 20(11):1117-1121 (1986).	
	D80	SINGH, "Consensus Statement from a Conference for the Management of Patients with Urea Cycle Disorders," Suppl. to J. Pediatrics (2001) 138(1):S1-S5.	
	D81	SUMMAR, M.L. et al. (October 2008, e-pub. July 17, 2008). "Diagnosis, Symptoms, Frequency and Mortality of 260 Patients with Urea Cycle Disorders From a 21-Year, Multicentre Study of Acute Hyperammonaemic Episodes," Acta Paediatr. 97:1420-1425.	
	D82	SUMMAR, M. et al. (2007). "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, September 4-7,2007, GSSIEM 2007, two pages.	
	D83	SWEDISH ORPHAN INTERNATIONAL. (January 12, 2007). "Urea Cycle Disorders an International Perspective," Poster, Symposium Swedish Orphan International, Barcelona, Spain, January 12, 2007, one page.	
	D84	TANNER, L. M., et al., "Nutrient Intake in Lysinuric Protein Intolerance," J. Inherit. Metab. Dis. 30:716-721 (2007).	

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				First Named Inventor	Bruce Scharschmidt
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(use as many sheets as necessary)				**Examiner Name**	Rao, Savitha M.
Sheet	10	of	10	**Attorney Docket Number**	HOR0026-201TC1-US

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	D85	THIBAULT, A., et al., "A Phase I and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer," Cancer Res. 54:1690-1694 (1994).	
	D86	THIBAULT, A., et al., "Phase I Study of Phenylacetate Administered Twice Daily to Patients with Cancer," Cancer 75:2932-2938 (1995).	
	D87	TUCHMAN, M. et al. (2008, e-pub. June 17, 2008). "Cross-Sectional Multicenter Study of Patients With Urea Cycle Disorders in the United States," Malec. Genetics Metab. 94:397-402.	
	D88	UMass Memorial Medical Center, Lab Updates, "Measurement of Ammonia in Blood." February 2007. Accessed at www.ummlabs.org/News/07Feb.pdf.	
	D89	WALSH et al., THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 8, pp. 4374-4381 (1990), "sn-1,2-Diacylgylcerol Kinase of Escherichia coli".	
	D90	WATERLOW, J.C. (March 1963). "The Partition of Nitrogen in the Urine of Malnourished Jamaican Infants," Am. J. of Clin. Nutrition 12:235-240.	
	D91	ZEITLIN, P.L. et al. (July 2002). "Evidence of CFTR Function in Cystic Fibrosis After System Administration of 4-Phenylbutyrate," Mol. Therapy 6(1):119-126.	

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EAST Search History

EAST Search History (Prior Art)

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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;	OR	OFF	2015/10/29 09:59

			USOCR; 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	65	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/12/15 10:24
S83	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	2015/12/15 10:24
S84	8	S83 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:24
S85	2	S84 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:24
S86	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/12/15 10:24
S87	30	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/12/15 10:24
S88	136	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:24
S89	17	S88 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:24
S90	17	S88 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:25
S91	1	"14816674".rlan. or ("14".src. and "816674".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:41
S92	5880	((A61K31/216 OR A61K9/0053 OR	US-PGPUB;	OR	OFF	2015/12/15

		G01N2800/085 OR G01N31/221 OR G01N33/4925 OR Y10T436/175383).CPC.)	USPAT; USOCR; DERWENT			10:42
S93	0	S92 with nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:42
S94	1629	S92 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:42
S95	93402	S94 an scavanging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:42
S96	1	S94 and scavanging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:42
S97	0	S94 and scavanger	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:42
S98	38	S92 and "urea cycle"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:43
S99	10	S92 and "glyceryl tri-[4-phenylbutyrate]"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:44
S100	0	"I20" and "glyceryl tri-[4-phenylbutyrate]"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2015/12/15 10:46

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S101	4229	((A61K31/216 OR A61K9/0053 OR G01N2800/085 OR G01N31/221 OR G01N33/4925 OR Y10T436/175383).CPC.)	US-PGPUB; USPAT	OR	OFF	2015/12/15 10:45
S102	709	S101 and urea	US-PGPUB; USPAT	OR	OFF	2015/12/15 10:45
S103	10	S102 and "glyceryl tri-[4-phenylbutyrate]"	US-PGPUB; USPAT	OR	OFF	2015/12/15 10:46

12/16/2015 8:12:36 AM
C:\Users\srao3\Documents\EAST\Autosave\~EASTAutoSave.wsp.asv

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14816674	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SAVITHA RAO	1621

CPC						
Symbol					**Type**	**Version**
A61K		31	/	216	F	2013-01-01
Y10T		436	/	175383	A	2015-01-15
A61K		9	/	0053	I	2013-01-01
G01N		31	/	221	I	2013-01-01
G01N		33	/	4925	I	2013-01-01
G01N		2800	/	085	A	2013-01-01
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CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	15	
/SAVITHA RAO/ Primary Examiner.Art Unit 1621	12/15/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14816674	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SAVITHA RAO	1621

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

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	15	
/SAVITHA RAO/ Primary Examiner.Art Unit 1621	12/15/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14816674	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SAVITHA RAO	1621

☒ Claims renumbered in the same order as presented by applicant	☐ CPA	☒ T.D.	☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 15	
/SAVITHA RAO/ Primary Examiner.Art Unit 1621 (Primary Examiner)	12/15/2015 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

U.S. Patent and Trademark Office

Part of Paper No. 20151215

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 12/23/2015
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.
14/816,674	08/03/2015	Bruce Scharschmidt	HOR0026-201TC1-US	9599

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	03/23/2016

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

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

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

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

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

(A) NAME OF ASSIGNEE: Horizon Therapeutics, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Deerfield, 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 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature /Lauren L. STEVENS/ Date 12-29-2015
Typed or printed name Lauren L. Stevens Registration No. 36691

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal

Application Number:	14816674
Filing Date:	03-Aug-2015
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Lauren Stevens/Vicki Truman
Attorney Docket Number:	HOR0026-201TC1-US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960

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

Electronic Acknowledgement Receipt	
EFS ID:	24485530
Application Number:	14816674
International Application Number:	
Confirmation Number:	9599
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Lauren Stevens/Vicki Truman
Filer Authorized By:	Lauren Stevens
Attorney Docket Number:	HOR0026-201TC1-US
Receipt Date:	29-DEC-2015
Filing Date:	03-AUG-2015
Time Stamp:	20:12:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$960
RAM confirmation Number	5895
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 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 1.20 (Post Issuance 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	Issue Fee Payment (PTO-85B)	20151229_Issue_Fee.pdf	991881 d12c96929cdb75bbdbb05bda71ad7dc0eb0d1ae3	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30759 2fa0c41d96ee56deaca52ff388a8e70feb717f7a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1022640		

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

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

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: March 12, 2012

(use as many sheets as necessary)

Sheet 2 of 13

Complete if Known	
Application Number	To Be Assigned
Filing Date	TBA
First Named Inventor	Bruce Scharschmidt
Art Unit	TBA
Examiner Name	TBA
Attorney Docket Number	HOR0026-201C1-US

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	F1	WO1994/22494	10-13-1994	The DuPont Merck Pharmaceutical Company		
	F2	WO2013/048558	04-04-2013	Hyperion Therapeutics, Inc.		
	F3	WO2013/158145	10-24-2013	Hyperion Therapeutics, Inc.		
	F4	WO2007/005633	1/2007			
	F5	WO2009/087474	7/16/2009	Akthelia Pharmaceuticals		
	F6	WO2012/028620	3/2012			

Change(s) applied to document, /J.L.B./ 1/4/2016

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D1	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).	
	D2	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.	
	D3	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).	
	D4	Barsotti, Measurement of Ammonia in Blood, 138 J. Pediatrics, S11-S20 (2001)	
	D5	Batshaw, et al., Treatment of Carbamyl Phosphate Synthetase Deficiency with Keto Analogues of Essential Amino Acids, 292 The New England J. Medicine, 1085□90 (1975)	
	D6	Batshaw, M. L. et. al., Alternative Pathway Therapy for Urea Cycle Disorder: Twenty Years Later, 138 J. Pediatrics S46 (2001).	

Examiner Signature		Date Considered	

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

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

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Approved for use through 03/31/2007. OMB 0651-0031
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: March 12, 2012

(use as many sheets as necessary)

Sheet 1 of 13

Complete if Known	
Application Number	To Be Assigned
Filing Date	TBA
First Named Inventor	Bruce Scharschmidt
Art Unit	TBA
Examiner Name	TBA
Attorney Docket Number	HOR0026-201C1-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication or Issue Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	P1	4,457,942	07-03-1984	Brusilow, S.W.	
Change(s) applied to document, /J.L.B./ 1/4/2016	P2	5,654,333	08-05-1997	The United States Of America As Represented By The Department Of Health And Human Services Samid	
	P3	8,094,521	01-10-2012	~~Nightengale Products LLC~~ Levy	
	P4	8,404,215	03-26-2013	~~Hyperion Therapeutics, Inc.~~ Scharschmidt et al.	
	P5	2003/0195255	10-16-2003	Marshall L. Summar	
	P6	2005/0273359	12-08-2005	Young, D.E.	
	P7	2010/0016207	01-21-2010	Wurtman, RJ et al	
	P8	2013/0281530	10-24-2013	Scharschmidt, B et al	
	P9	2014/0142186	05-22-2014	~~Hyperion Therapeutics, Inc.~~ Scharschmidt et al.	
	P10	6,219,567	4/17/2001	EGGERS	
	P11	8,642,012	2/4/2014	SCHARSCHMIDT	
	P12	2010/0008859	1/14/2010	SCHARSCHMIDT	
	P13	2012/0022157	1/26/2012	SCHARSCHMIDT	
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Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 10

Complete if Known	
Application Number	14/816674
Filing Date	8/03/2015
First Named Inventor	Bruce Scharschmidt
Art Unit	1621
Examiner Name	Rao, Savitha M.
Attorney Docket Number	HOR0026-201TC1-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication or Issue Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	P1	2004/0229948	11/18/2004	SUMMAR et al.	
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Change(s) applied to document,
/N.G./
1/6/2016

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	F1	WO2005/053607	06/16/2005	MEDICIS PHARMACEUTICAL CORP.		
	F2	WO2006/056794	06/01/2006	UCL BUSINESS PLC		
	F3	WO2009/134460	11/05/2009	HYPERION THERAPEUTICS		
	F4	WO2010/025303	03/04/2010	HYPERION THERAPEUTICS		

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/816,674	02/09/2016	9254278	HOR0026-201TC1-US	9599

101325 7590 01/20/2016

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

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

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