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.

Electronic Acknowledgement Receipt	
EFS ID:	12273906
Application Number:	13417137
International Application Number:	
Confirmation Number:	6423
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Patrick D. Morris/Colleen Kirchner
Filer Authorized By:	Patrick D. Morris
Attorney Docket Number:	79532.8003.US02
Receipt Date:	09-MAR-2012
Filing Date:	
Time Stamp:	20:28:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1025
RAM confirmation Number	6954
Deposit Account	502586
Authorized User	
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 1.19 (Document supply fees) Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance 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	Transmittal of New Application	Transmittal.pdf	18577 1cfd2319bc7a6a29a23939d99abdf90fd286e9eb9e	no	2
Warnings:					
Information:					
2		US_Specification.pdf	407442 826a6226d6be4af33c5624c1715e9d929e34b1e14	yes	38

Multipart Description/PDF files in .zip description

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

Warnings:					
Information:					
3	Petition to make special based on Age/ Health	1PetitiontoMakeSpecial.pdf	28687 be009fbfb1b142993a8d25ef17815b6f7b9d1002	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	38065 662566fe500c378afc686d59086ba61210a15e6	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	492771		

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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.

What is claimed is:

1. A method for determining whether to increase a dosage of a nitrogen scavenging drug in a subject currently receiving the nitrogen scavenging drug, comprising:

a) measuring a fasting blood ammonia level for the subject; and

b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level to determine whether to increase the dosage of a nitrogen scavenging drug, wherein the dosage needs to be increased if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.

2. A method for determining whether to administer a nitrogen scavenging drug to a subject having a nitrogen retention disorder comprising:

a) measuring a fasting blood ammonia level for the subject; and

b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level to determine whether to administer a nitrogen scavenging drug to the subject, wherein a nitrogen scavenging drug needs to be administered to the subject if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.

3. A method of treating a subject with a nitrogen retention disorder who has previously been administered a nitrogen scavenging drug comprising:

a) measuring a fasting blood ammonia level for the subject; and

b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level and administering an increased dosage of the nitrogen scavenging drug if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.

4. The method of claim 1, further comprising:

c) administering an increased dosage of the nitrogen scavenging drug if the need exists.

5. The method of any of claims 1-3, wherein the nitrogen retention disorder is selected from the group consisting of a urea cycle disorder and hepatic encephalopathy.

6. The method of any of claims 1-3, wherein the nitrogen scavenging drug is a PAA prodrug.

7. The method of claim 6, wherein the PAA prodrug is selected from the group consisting of glyceryl tri-[4-phenylbutyrate] (HPN-100), phenylbutyric acid (PBA), sodium PBA (NaPBA), and a combination of two or more of HPN-100, PBA, and NaPBA.

8. The method of any of claims 1-3, wherein the nitrogen scavenging drug is sodium benzoate.

9. The method of claim 3 or 4, wherein administering an increased dosage of the nitrogen scavenging drug produces a normal average daily ammonia level in the subject.

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

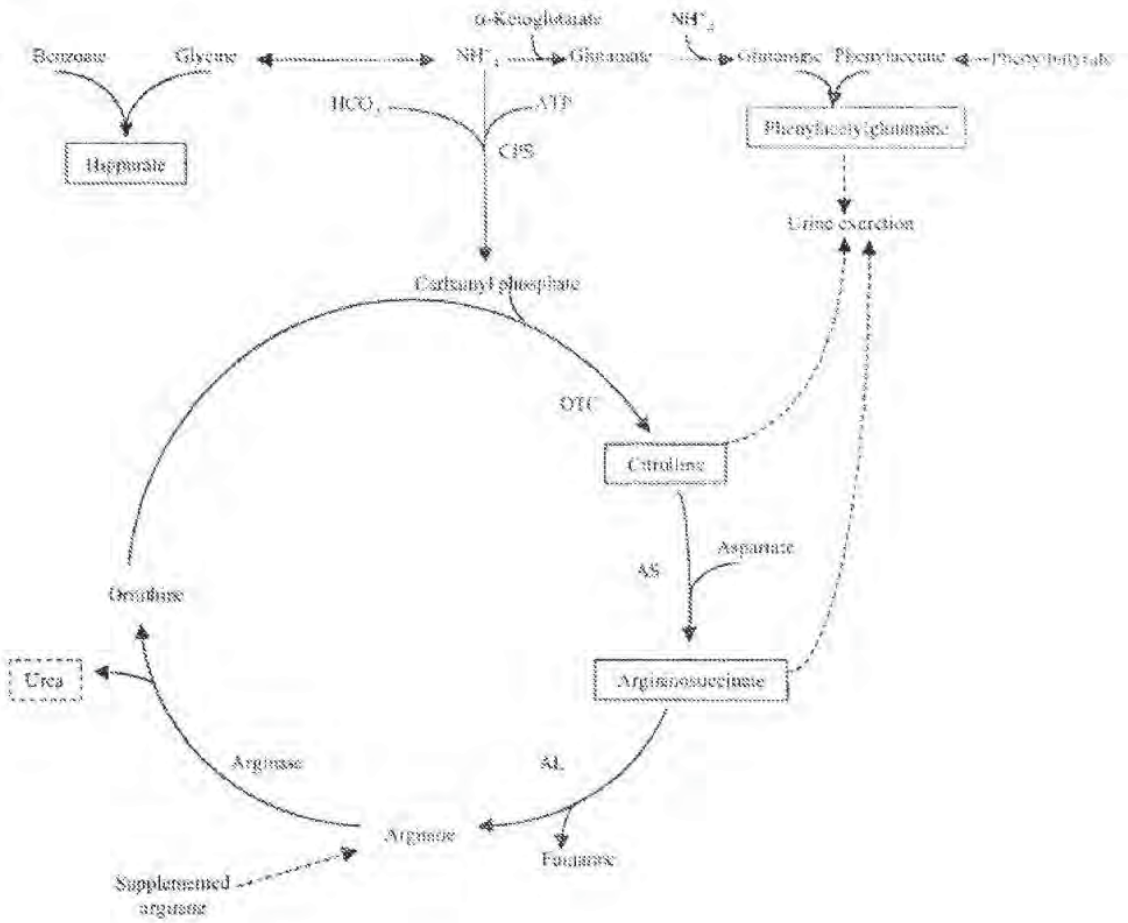
11. The method of any of claims 1-3, wherein the upper limit of normal blood ammonia level is 35 μmol/L.

12. The method of claim 6, further comprising:

c) measuring urinary PAGN excretion; and

e) determining an effective dosage of the PAA prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60-75%.

Figure 1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Benzoate
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NH^+_4
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Hippurate
CPS
Phenylacetylglutamine
Urine excretion
Carbamyl phosphate
OTC
Citrulline
Aspartate
AS
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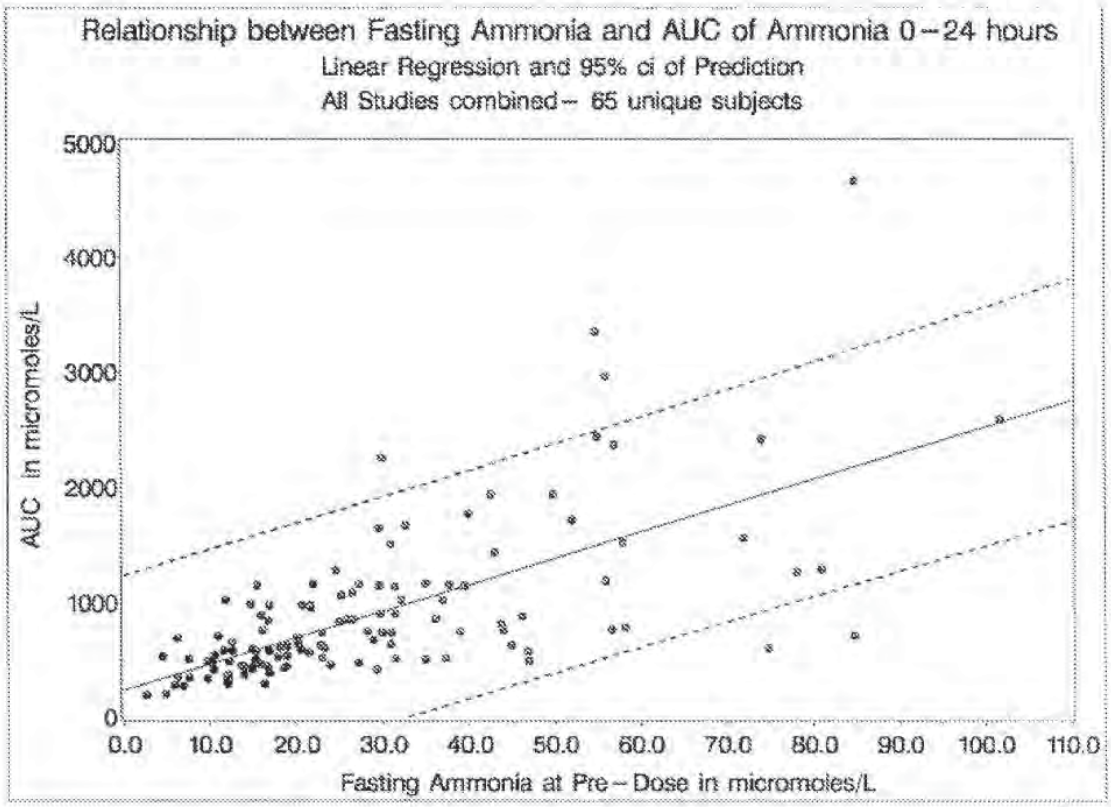
Urea
Argininosuccinate
Arginase
AL
Arginine
Fumarate
Supplemented arginine

Figure 2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Linear Regression and 95% ci of Prediction
All Studies combined – 65 unique subjects
AUC in micromoles/L
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3000
2000
1000
0
0.0
10.0
20.0
30.0
40.0
50.0
60.0
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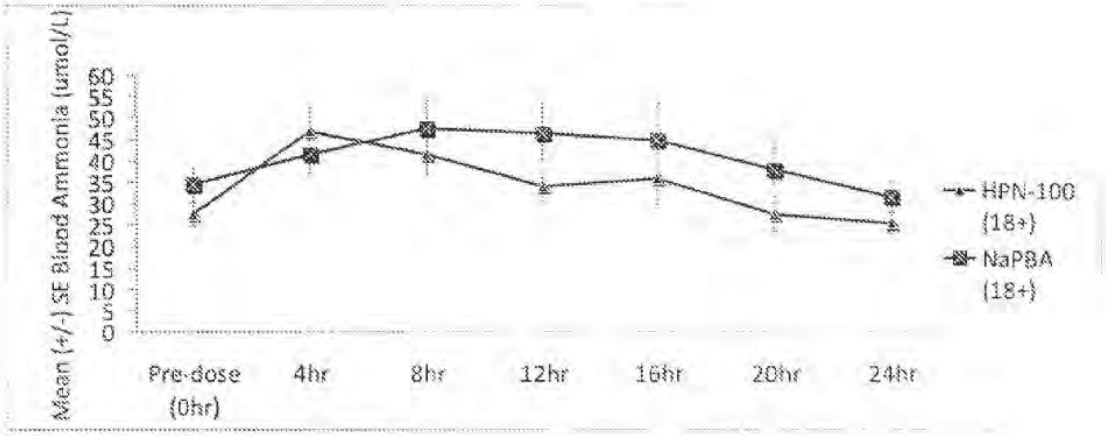
80.0
90.0
100.0
110.0
Fasting Ammonia at Pre – Dose in micromoles/L

Figure 3

A.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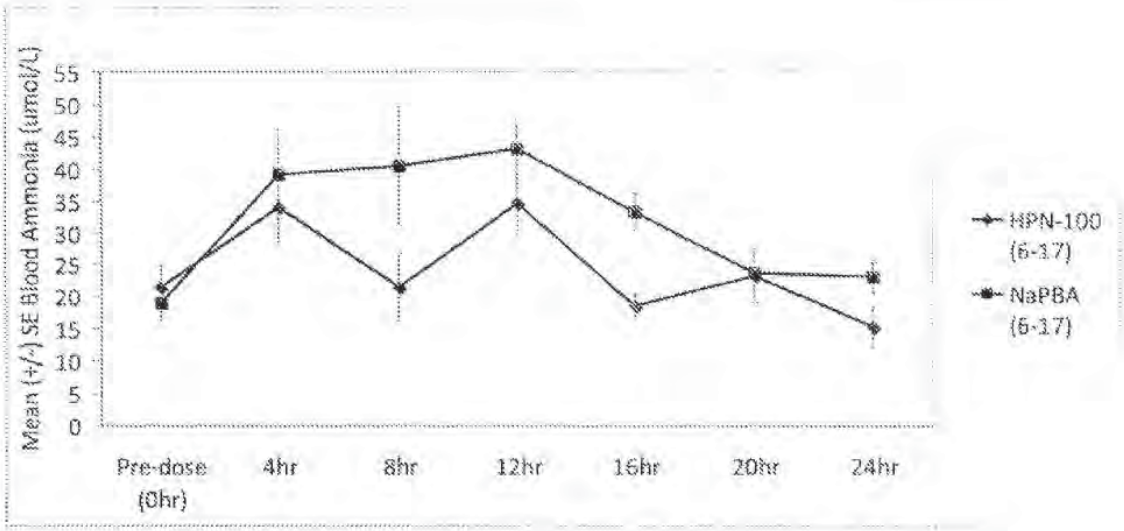
50
45
40
35
30
25
20
15
10
5
0
Pre-dose (0hr)
4hr
8hr
12hr
16hr
20hr
24hr
HPN-100 (18+)
NaPBA (18+)

B.


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

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Information:					
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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:	Patrick D. Morris/Colleen Kirchner
Attorney Docket Number:	79532.8003.US02

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	95	95
Utility Search Fee	2111	1	310	310
Utility Examination Fee	2311	1	125	125
Pages:				
Claims:				
Claims in excess of 20	2202	9	30	270
Multiple dependent claims	2203	1	225	225
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1025

Doc code : PET.OP.AGE
Description : Petition to make special based on Age/Health

PTO/SB/130 (07-09)
Approved for use through 07/31/2012. OMB 0651- 0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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PETITION TO MAKE SPECIAL BASED ON AGE FOR ADVANCEMENT OF EXAMINATION UNDER 37 CFR 1.102(c)(1)					
Application Information					
Application Number		Confirmation Number		Filing Date	2012-03-09
Attorney Docket Number (optional)	79532.8003.US02	Art Unit		Examiner	
First Named Inventor	Bruce Scharschmidt				
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS				

Attention: Office of Petitions
An application may be made special for advancement of examination upon filing of a petition showing that the applicant is 65 years of age, or more. No fee is required with such a petition. See 37 CFR 1.102(c)(1) and MPEP 708.02 (IV).

APPLICANT HEREBY PETITIONS TO MAKE SPECIAL FOR ADVANCEMENT OF EXAMINATION IN THIS APPLICATION UNDER 37 CFR 1.102(c)(1) and MPEP 708.02 (IV) ON THE BASIS OF THE APPLICANT'S AGE.

A grantable petition requires one of the following items:
(1) Statement by one named inventor in the application that he/she is 65 years of age, or more; or
(2) Certification by a registered attorney/agent having evidence such as a birth certificate, passport, driver's license, etc. showing one named inventor in the application is 65 years of age, or more.

Name of Inventor who is 65 years of age, or older

Given Name	Middle Name	Family Name	Suffix
Bruce		Scharschmidt	

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18.
Please see 37 CFR 1.4(d) for the format of the signature.

Select (1) or (2) :

○ (1) I am an inventor in this application and I am 65 years of age, or more.

◉ (2) I am an attorney or agent registered to practice before the Patent and Trademark Office, and I certify that I am in possession of evidence, and will retain such in the application file record, showing that the inventor listed above is 65 years of age, or more.

Signature	/Patrick D. Morris/	Date (YYYY-MM-DD)	2012-03-09
Name	Patrick D. Morris	Registration Number	53351

PTO/SB/130 (07-09)
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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 Fr eedom of Information Act requires disclosure of these records.

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 indivi duals.

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.

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METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

RELATED APPLICATIONS

[0001] The present application 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).

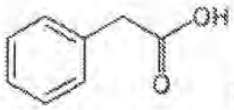
[0004] Hepatic encephalopathy (HE) refers to a spectrum of neurologic signs and symptoms believed to result from hyperammonemia, which frequently occur in subjects with cirrhosis or

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.

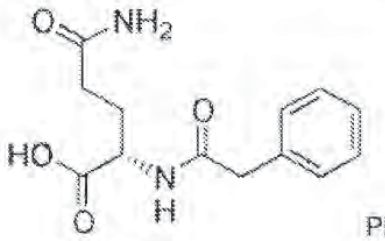
[0005] Subjects with nitrogen retention disorders whose ammonia levels and/or symptoms are not adequately controlled by dietary restriction of protein and/or dietary supplements are generally treated with nitrogen scavenging agents such as sodium phenylbutyrate (NaPBA, approved in the United States as 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 1.5 ULN, and a 93% chance (with a 95% confidence

interval of 78% to 100%) of never having an ammonia of more than 100 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-100 per day. Patient B is treated with 3.5mL of HPN-100 3 times a day for at least 7 days, and returns for additional blood draws. Her fasting blood ammonia level at this time is 17 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.

REFERENCES

1. Brusilow Science 207:659 (1980)
2. Brusilow Pediatr Res 29:147 (1991)
3. Diaz Mol Genet Metab 102:276 (2011)
4. Gropman Mol Genet Metab 94:52 (2008a)

5. Gropman Mol Genet Metab 95:21 (2008b)
6. Lee Mol Genet Metab 100:221 (2010)
7. Liang Biometrika 73:13 (1986)
8. Lichter-Konecki Mol Genet Metab 103:323 (2011)
9. McGuire Hepatology 51:2077 (2010)
10. Thibault Cancer Res 54:1690 (1994)
11. Thibault Cancer 75:2932 (1995)

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

NEW APPLICATION TRANSMITTAL - UTILITY

Sir:

Transmitted herewith for filing is a utility patent application:

Inventor(s): Bruce Scharschmidt
Masoud Mokhtarani

Title: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

I. PAPERS ENCLOSED HEREWITH FOR FILING UNDER 37 CFR § 1.53(b):

32 Page(s) of Written Description
2 Page(s) Claims
1 Page(s) Abstract
3 Sheets of Drawings
Sheets of Sequence Listing

II. ADDITIONAL PAPERS ENCLOSED IN CONNECTION WITH THIS FILING:

☒ Petition to Make Special Based on Age for Advancement of Examination Under 37 CFR 1.102(c)(1)

III. U.S. PRIORITY:

The present application 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.

IV. FEES:

☒ Applicant claims small entity status pursuant to 37 CFR § 1.27
☒ This application is being filed without Declaration under 37 CFR § 1.53.

V. CORRESPONDENCE ADDRESS

Please send all correspondence to Customer Number 34055.

Perkins Coie LLP
Patent – LA
P.O. Box 1208
Seattle, WA 98111-1208
Phone: (310) 788-9900
Fax: (206) 332-7198

Please direct all inquiries to Patrick Morris at the above customer number.

Respectfully submitted,

PERKINS COIE LLP

Dated: March 9, 2012

By: /Patrick D. Morris/
Patrick D, Morris
Reg. No. 53,351

Electronic Acknowledgement Receipt	
EFS ID:	12273906
Application Number:	13417137
International Application Number:	
Confirmation Number:	6423
Adjustment date: 03/22/2012 CCETIN 03/12/2012 INTEFSW 00006954 502586 13417137 04 FC:2202 270.00 CR **Title of Invention:** 03/22/2012 CCETIN 00000021 502586 13417137 01 FC:2202 210.00 DA	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Patrick D. Morris/Colleen Kirchner
Filer Authorized By:	Patrick D. Morris
Attorney Docket Number:	79532.8003.US02
Receipt Date:	09-MAR-2012
Filing Date:	
Time Stamp:	20:28:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1025
RAM confirmation Number	6954
Deposit Account	502586
Authorized User	
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)	

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
13417137	

Applicant(s) Bruce SCHARSCHMIDT

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
2	1					
3	1					
4		1				
5		3				
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Total Indep	3		0		0	
Total Depend	24	↵	0	↵	0	↵
Total Claims	27		0		0	

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	Indep	Depend	Indep	Depend	Indep	Depend
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/417,137

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	95		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	310		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	125		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	27 minus 20 =	* 7	x 30 =	210	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x 125 =	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))				225			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	965		TOTAL	

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($)	ADDITIONAL FEE($)		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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/417,137	03/09/2012	1629	965	79532.8003.US02	12	3

CONFIRMATION NO. 6423

34055
PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE, WA 98111-1208

FILING RECEIPT

OC000000053293071

Date Mailed: 03/26/2012

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**

Applicant(s)

Bruce SCHARSCHMIDT, Residence Not Provided;
Masoud Mokhtarani, Residence Not Provided;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/564,668 11/29/2011
and claims benefit of 61/542,100 09/30/2011

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 03/22/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/417,137**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **

Title

METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

Preliminary Class

514

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 (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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

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

NOT GRANTED

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

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/417,137	03/09/2012	Bruce SCHARSCHMIDT	79532.8003.US02

CONFIRMATION NO. 6423

34055
PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE, WA 98111-1208

FORMALITIES LETTER

OC000000053293072

Date Mailed: 03/26/2012

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings have a line quality that is too light to be reproduced (weight of all lines and letters must be heavy enough to permit adequate reproduction) or text that is illegible (reference characters, sheet numbers, and view numbers must be plain and legible) see 37 CFR 1.84(l) and (p)(1)); See Figure(s) 1,3.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- A surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**65** for a small entity in compliance with 37 CFR 1.27, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $**65** for a small entity
- $**65** Surcharge.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/rerry/

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

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PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE WA 98111-1208

MAILED
APR 04 2012
OFFICE OF PETITIONS

In re Application of :
Bruce Scharschmidt, et al. :
Application No. 13/417,137 : DECISION ON PETITION
Filed: March 9, 2012 : TO MAKE SPECIAL UNDER
Attorney Docket No. 79532.8003.US02 : 37 CFR 1.102(c)(1)
:

This is a decision on the petition under 37 CFR 1.102(c)(1), filed March 9, 2012, to make the above-identified application special based on applicant's age as set forth in M.P.E.P. § 708.02, Section IV.

The petition is **GRANTED**.

A grantable petition to make an application special under 37 CFR 1.102(c)(1) and MPEP § 708.02, Section IV: Applicant's Age must be accompanied by evidence showing that at least one of the applicants is 65 years of age, or more, such as a birth certificate or a statement by applicant. No fee is required

The instant petition includes a statement from the inventor, Bruce Scharschmidt, declaring that he is 65 years of age or older. Accordingly, the above-identified application has been accorded "special" status.

Telephone inquiries concerning this decision should be directed to Terri Johnson at 571-272-2991.

All other inquiries concerning either the examination or status of the application should be directed to the Technology Center.

The application is being forwarded to the Technology Center Art Unit 1629 for action on the merits commensurate with this decision.

/Terri Johnson/
Terri Johnson
Petitions Examiner
Office of Petitions

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: BRUCE SCHARSCHMIDT ET AL.	CONFIRMATION NO.: 6423
APPLICATION NO.: 13/417,137	ART UNIT: 1629
FILING DATE: MARCH 9, 2012	
FOR: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

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

Sir:

In response to the Notice to File Missing Parts of Nonprovisional Application mailed on March 26, 2012, applicants submit the following:

☒ an executed Declaration of Inventorship;

☒ an executed Power of Attorney by Assignee;

☒ Replacement Drawings (3 sheets); and

☒ an Information Disclosure Statement (Form PTO/SB/08a) with cited references.

1. Authorization for Extensions of Time Under 37 C.F.R. § 1.136 (a)(3)

Applicants petition for an Extension of Time if necessary for timely filing of this Response. The Commissioner is authorized to treat this or any future reply requiring a Petition for Extension of Time under 37 C.F.R. § 1.136 (a)(3) for its timely submission as incorporating a petition herefore for the appropriate length of time. Please charge all required extension of time fees in this application to Deposit Account No. 50-2586.

2. Fee Calculation and Payment

For:	(Col. 1) No. Filed	(Col. 2) No. Extra	Small Entity			Other Than a Small Entity	
			Rate	Fee		Rate	Fee
Filing Fee			$95	$	or	$380	$
Search Fee			$310	$	or	$620	$
Examination Fee			$125	$	or	$250	$
Total Claims	– 20		X $30=	$	or	X $60=	$
Independent Claims	– 3		X $125=	$	or	X $250=	$
☐ Multiple Dependent Claim Presented			+ $225=	$	or	+ $450=	$
Application Size Fee – for each additional 50 sheets that exceeds 100 sheets			X $155=	$	or	X $310=	$
Missing Parts Surcharge			$65.00	$65.00		$130	$
Extension of Time Fee				$			$
*If the difference in Col. 1 is less than zero, enter "0" in Col. 2.			TOTAL	$	or	TOTAL	**$**

☒ Please charge Deposit Account No. 50-2586 in the amount of $65.00 for the requisite fees.

☒ Please charge any deficiency or credit to Deposit Account No. 50-2586.

Dated: May 16, 2012

Respectfully submitted,

PERKINS COIE LLP

By: /Patrick D. Morris/
Patrick D. Morris, Ph.D.
Reg. No. 53,351

Correspondence Address:
Customer No. 34055
Perkins Coie LLP
Patent - LA
P.O. Box 1208
Seattle, WA 98111-1208
Phone: (310) 788-9900
Fax: (206) 332-7198

Figure 1

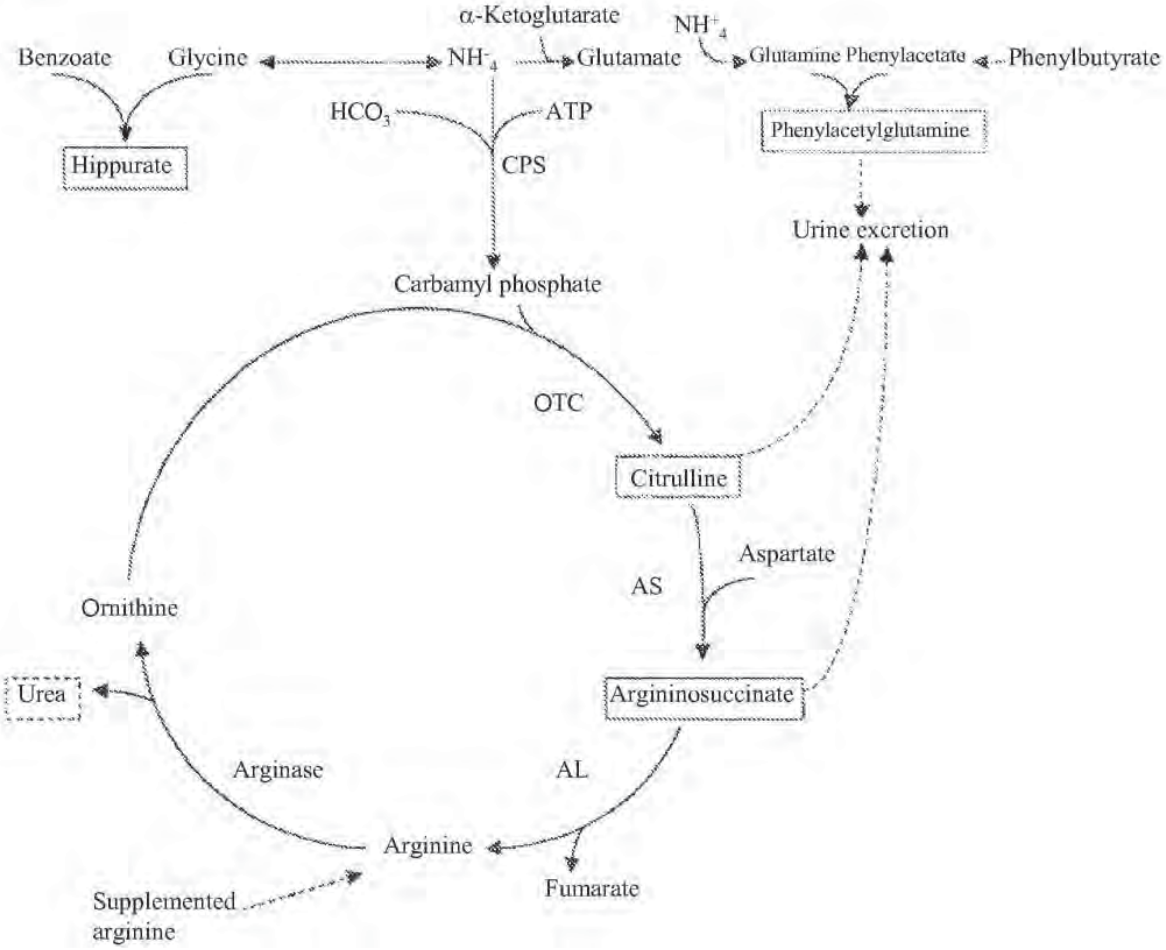
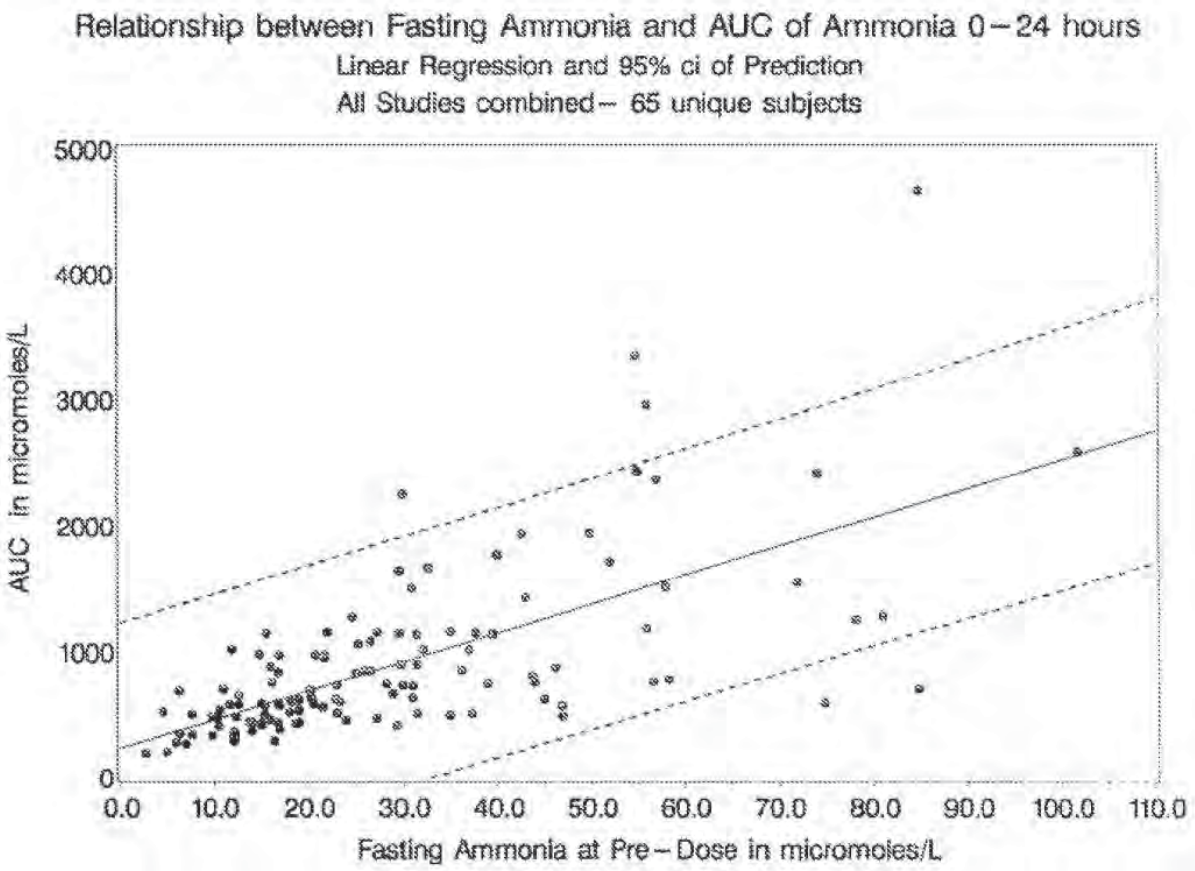

α-Ketoglutarate
NH^+_4
Benzoate
Glycine
NH^-_4
Glutamate
Glutamine
Phenylacetate
Phenylbutyrate
HCO_3
ATP
CPS
Hippurate
Phenylacetylglutamine
Urine excretion
Carbamyl phosphate
OTC
Citrulline
Aspartate
AS
Ornithine
Urea
Argininosuccinate
Arginase
AL
Arginine
Fumarate
Supplemented arginine

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
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1000
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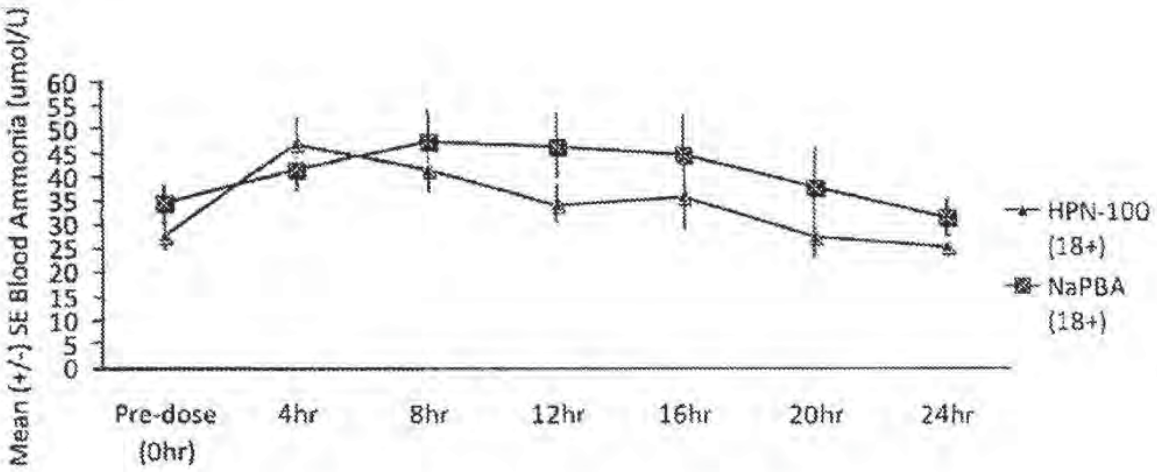
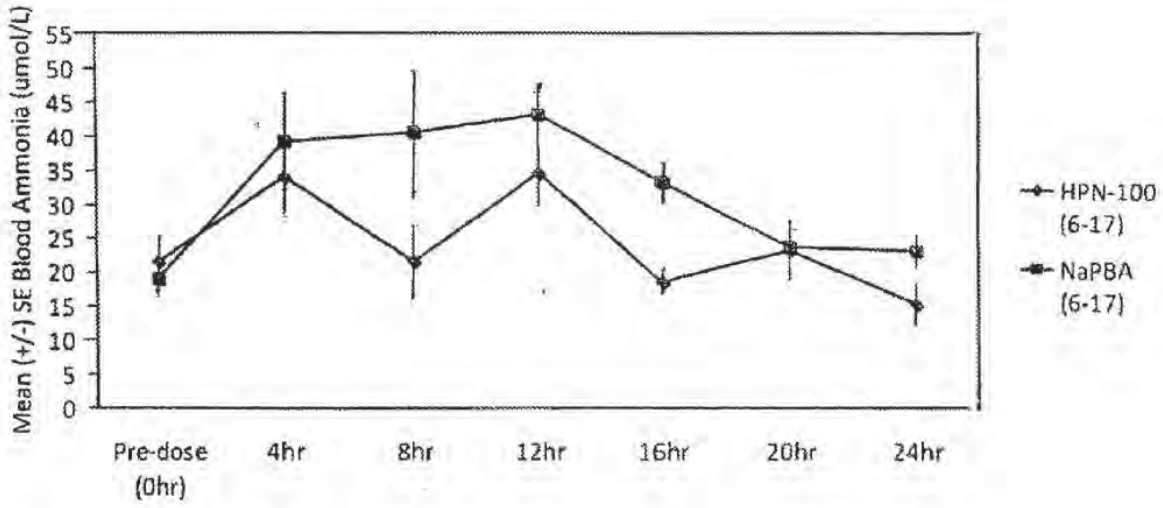
100.0
110.0
Fasting Ammonia at Pre – Dose in micromoles/L

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 Acknowledgement Receipt	
EFS ID:	12798370
Application Number:	13417137
International Application Number:	
Confirmation Number:	6423
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Patrick D. Morris/Colleen Kirchner
Filer Authorized By:	Patrick D. Morris
Attorney Docket Number:	79532.8003.US02
Receipt Date:	16-MAY-2012
Filing Date:	09-MAR-2012
Time Stamp:	19:20:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$65
RAM confirmation Number	8260
Deposit Account	502586
Authorized User	
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 1.17 (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	Applicant Response to Pre-Exam Formalities Notice	MPResponse.pdf	91043 de866851f1597f65fc545c86cf7469eb1c50fc0fc	no	2
Warnings:					
Information:					
2	Oath or Declaration filed	Declaration.pdf	603747 c740d668233caf53472350a3e9a2af33d39d0b285	no	2
Warnings:					
Information:					
3	Power of Attorney	POA.pdf	107837 723cfdc9504f50f1c2313ab828eb07e936c2430b	no	2
Warnings:					
Information:					
4	Drawings-only black and white line drawings	ReplacementDrawings.pdf	475055 161e93435f3354490e110c408f5e7ccc95ff35fd	no	3
Warnings:					
Information:					
5	Transmittal Letter	IDSTransmittal.pdf	72270 f81947a417cafc53060cd980c583a55d0259d969	no	3
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Form (SB08)	IDSForm.pdf	140927 37ddd347ddf114b625181d719046f5ad9d554471	no	10
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
7	Non Patent Literature	Liang.pdf	2034880 cb2f1d342134493252f297648bfe002fa89f3175	no	10
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	30356 b79ad12b4ba80fa419dcf7f4d84031a03928cc2	no	2
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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

New International Application Filed with the USPTO as a Receiving Office
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Electronic Patent Application Fee Transmittal

Application Number:	13417137
Filing Date:	09-Mar-2012
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
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Attorney Docket Number:	79532.8003.US02

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	2051	1	65	65
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**65**

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				First Named Inventor	Bruce SCHARSCHMIDT
				Group Art Unit	1629
				Examiner Name	To be assigned
Sheet	1	of	10	Attorney Docket No.	79532.8003.US02

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	U.S. Patent or Application NUMBER	Kind Code (if known)	Name of Patentee or Inventor of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Figures Appear
	A1	2004/0229948	A1	SUMMAR et al.	11/18/2004	
	A2	2006/0135612	A1	FERRANTE	06/22/2006	
	A3	2008/119554	A1	JALAN et al.	05/22/2008	
	A4	4,284,647		BRUSILOW et al.	08/18/1981	
	A5	5,968,979		BRUSILOW	10/19/1999	
	A6	6,050,510	A	BONNEWITZ	05/09/2000	
	A7	6,083,984		BRUSILOW	07/04/2000	

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Examiner Initial	Cite No.	Foreign Patent or Application Office	NUMBER	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Figures Appear	T
	B1	WO	2005/053607	A1	MEDICIS PHARMACEUTICAL CORP.	06/16/2005		
	B2	WO	2006/056794		UCL BUSINESS PLC	06/01/2006		
	B3	WO	2009/087474		AKTHELIA PHARMACEUTICALS	07/16/2009		
	B4	WO	2009/134460	A1	HYPERION THERAPEUTICS	11/05/2009		
	B5	WO	2010/0250303	A1	HYPERION THERAPEUTICS	03/04/2010		

OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS

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	C1	AMBROSE, A.M. et al. (1933). "Further Studies on the Detoxification of Phenylacetic Acid," J. Bio. Chem. 101:669-675.	
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				Examiner Name	To be assigned
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	C3	BATSHAW, M.L. et al. (August 1981). "New Approaches to the Diagnosis and Treatment of Inborn Errors of Urea Synthesis," Pediatrics 68(2):290-297.	
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	C23	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.	
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	C25	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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	C28	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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	C45	KASUMOV, T., et al., "New Secondary Metabolites of Phenylbutyrate in Humans and Rats," Drug Metabolism and Disposition (2004) 32(1):10-19.	
	C46	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.	
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	C48	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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	C50	LEE, B. et al. (August 2008). "Preliminary Data on Adult Patients with Urea Cycle Disorders (UCD) in an Open-Label, Switch-Over, Dose-Escalation Study Comparing a New Ammonia Scavenger, Glyceryl Tri (4-Phenylbutyrate) [HPN - 100], to Buphenyl® (Sodium Phenylbutyrate [PBAj)," abstract presented at SSIEM 2008, Lisbon, Portugal, one page.	
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	C57	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).	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO-1449 (Modified) (Use several sheets if necessary)				COMPLETE IF KNOWN	
				Application Number	13/417,137
				Confirmation Number	6423
				Filing Date	2012-03-09
				First Named Inventor	Bruce SCHARSCHMIDT
				Group Art Unit	1629
				Examiner Name	To be assigned
Sheet	8	of	10	Attorney Docket No.	79532.8003.US02

OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	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
	C58	MANSOUR, A. et al. (October 1997). "Abdominal Operations in Patients with Cirrhosis: Still A Major Surgical Challenge," Surqerv 122(4):730-735. (Abstract Only.)	
	C59	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.	
	C60	MCGUIRE, B. M., et al., "Pharmacology and Safety of Glycerol Phenylbutyrate in Healthy Adults and Adults with Cirrhosis," Hepatol. 51:2077-2085 (2010).	
	C61	MCGUIRE, B.M. et al. (2009). "Pharmacokinetic (PK) and Safety Analyses of a Novel Ammonia-Reducing Agent in Healthy Adults and Patients with Cirrhosis," Hyperion Therapeutics, poster, one page.	
	C62	MCGUIRE, B.M. et al. (May 2009). "Pharmacokinetic (PK) and Safety Analyses of a Novel Ammonia-Reducing Agent in Healthy Adults and Patients with Cirrhosis," abstract presented at DDW, May 2009, two pages.	
	C63	MCGUIRE, B. et al. (April 2008). "Pharmacokinetic Safety Study of Sodium Phenylacetate and Sodium Benzoate Administered to Subjects With Hepatic Impairments,' Liver International 28:743. (Abstract Only).	
	C64	MCGUIRE, B. et al. (April 2008). "Pharmacokeinetic (PK) Safety Study of Sodium Phenylacetate and Sodium Benzoate Administered to Subjects with Hepatic Impairment," abstract of The13th International Symposium, Abano (Padova), Italy, April 28-May 1,2008, two pages.	
	C65	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.	
	C66	PISCITELLI, S.C. et al. (1995). "Disposition of Phenyl butyrate and its Metabolites, Phenylacetete and Phenylacetylglutamine," J. Clin. Pharmacal. 35:368-373.	
	C67	PROPST, A. et al. (August 1995). "Prognosis and Life Expectancy in Chronic Liver Disease," Dig Dis Sci 40(8):1805-1815. (Abstract Only).	

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not criteria 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 application(s).

INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO-1449 (Modified) (Use several sheets if necessary)				COMPLETE IF KNOWN	
				Application Number	13/417,137
				Confirmation Number	6423
				Filing Date	2012-03-09
				First Named Inventor	Bruce SCHARSCHMIDT
				Group Art Unit	1629
				Examiner Name	To be assigned
Sheet	9	of	10	Attorney Docket No.	79532.8003.US02

OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	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
	C68	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).	
	C69	RUDMAN, D., et al., "Maximal Rates of Excretion and Synthesis of Urea in Normal and Cirrhotic Subjects," J. Clin. Invest. (1973) 52:2241-2249.	
	C70	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.	
	C71	SIMELL, O., et al., "Waste Nitrogen Excretion Via Amino Acid Acylation: Benzoate and Phenylacetate in Lysinuric Protein Intolerance," Pediatr. Res. 20(11):1117-1121 (1986).	
	C72	SINGH, "Consensus Statement from a Conference for the Management of Patients with Urea Cycle Disorders," Suppl. to J. Pediatrics (2001) 138(1):S1-S5.	
	C73	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.	
	C74	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.	
	C75	SWEDISH ORPHAN INTERNATIONAL. (January 12, 2007). "Urea Cycle Disorders an International Perspective," Poster, Symposium Swedish Orphan International, Barcelona, Spain, January 12, 2007, one page.	
	C76	TANNER, L. M., et al., "Nutrient Intake in Lysinuric Protein Intolerance," J. Inherit. Metab. Dis. 30:716-721 (2007).	
	C77	THIBAULT, A., et al., "A Phase I and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer," Cancer Res. 54:1690-1694 (1994).	

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not criteria 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 application(s).

INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO-1449 (Modified) (Use several sheets if necessary)				COMPLETE IF KNOWN	
				Application Number	13/417,137
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Sheet	10	of	10	Attorney Docket No.	79532.8003.US02

OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	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
	C78	THIBAULT, A., et al., "Phase I Study of Phenylacetate Administered Twice Daily to Patients with Cancer," Cancer 75:2932-2938 (1995).	
	C79	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.	
	C80	WATERLOW, J.C. (March 1963). "The Partition of Nitrogen in the Urine of Malnourished Jamaican Infants," Am. J. of Clin. Nutrition 12:235-240.	
	C81	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	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not criteria 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 application(s).

UTILITY DECLARATION OF INVENTORSHIP

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS**, the specification of which

(Check One) ☐ is attached hereto OR
☒ was deposited on March 9, 2012 and accorded United States Application No. 13/417,137.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Date of Filing	Priority Claimed Yes	Priority Claimed No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date
61/542,100	September 30, 2011
61/564,668	November 29, 2011

I hereby claim the benefit under Title 35, United States Code § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date	Status-Patented, Pending or Abandoned

I further 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 are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

201	FULL NAME OF INVENTOR	FIRST Name Bruce	MIDDLE Initial	LAST Name SCHARSCHMIDT	
	RESIDENCE & CITIZENSHIP	City San Francisco	State or Foreign Country CA	Country of Citizenship USA	
	POST OFFICE ADDRESS	45 St. Francis Boulevard	City San Francisco	State or Country CA	Zip Code 94127
INVENTOR'S SIGNATURE				DATE 4/18/12	

202	FULL NAME OF INVENTOR	FIRST Name Masoud	MIDDLE Initial	LAST Name MOKHTARANI	
	RESIDENCE & CITIZENSHIP	City Walnut Creek	State or Foreign Country CA	Country of Citizenship USA	
	POST OFFICE ADDRESS	725 Castle Rock Road	City Walnut Creek	State or Country CA	Zip Code 94598
INVENTOR'S SIGNATURE				DATE 4/17/2012	

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: BRUCE SCHARSCHMIDT ET AL.	CONFIRMATION NO.: 6423
APPLICATION NO.: 13/417,137	ART UNIT: 1629
FILING DATE: MARCH 9, 2012	
FOR: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS	

Power of Attorney by Assignee and Certification Under 37 C.F.R. § 3.73(b)

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

Sir:

I, the undersigned, acting on behalf of the Assignee of the entire right, title and interest in the above-identified patent application, by virtue of an Assignment recorded on April 9, 2012, at Reel/Frame 028014/0894, appoint the attorneys and agents listed below to prosecute this patent and transact all business with the U.S. Patent and Trademark Office in connection therewith. This appointment is to the exclusion of the inventor(s) and their attorney(s) and agent(s) in accordance with the provisions of 37 C.F.R. § 3.71.

All prior powers of attorney for this application are hereby revoked. The Assignee hereby appoints all of the registered practitioners identified by Customer Number 34055:

Customer Number 34055
Perkins Coie LLP
Patent – LA
P.O. Box 1208
Seattle, WA 98111-1208
Phone: (310) 788-9900
Fax: (206) 332-7198

Please direct all inquires to Patrick D. Morris at the above Customer Number.

In accordance with 37 C.F.R. § 3.73(b), I hereby certify that I am empowered to act on behalf of the Assignee. To the best of my knowledge and belief, title is in the Assignee, as evidenced by the Assignment noted above.

I further declare 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 Title 18, USC § 1001 and that such willful false statements may jeopardize the validity of this patent.

ASSIGNEE: HYPERION THERAPEUTICS, INC.

Signature: [signature]

Typed Name: Jeffrey Farrow

Title: CFO

Date: 4/17/12

Address: 601 Gateway Blvd., Suite 200, South San Francisco, CA 94080

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	BRUCE SCHARSCHMIDT	ART UNIT:	1629
APPLICATION NO.:	13/417,137	CONF. NO:	6423
FILED:	MARCH 9, 2012		
FOR:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS		

Information Disclosure Statement Within Three Months of Application Filing or Before First Action – 37 C.F.R. § 1.97(b)

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

Sir:

1. Timing of Submission

This information disclosure is being filed within three months of the filing date of this application or date of entry into the national stage of an international application or before the mailing date of a first Office action on the merits, whichever occurs last [37 C.F.R. § 1.97(b)]. The references listed on the enclosed Form PTO-1449 (modified) may be material to the examination of this application; the Examiner is requested to make them of record in the application.

2. Cited Information

☒ Copies of the following references are enclosed:

☐ All cited references
☒ References marked by asterisks
☐ The following:

☒ Copies of the following references can be found in related U.S. Application No. 12/350,111:

- ☒ All cited references except those marked by asterisks
- ☐ References marked by asterisks
- ☐ The following:

☒ This application was filed after 30 June 2003 and no copies of U.S. patents nor published applications are enclosed (See Notice of Deputy Commissioner Kunin on 11 July 2003).

☐ The following references are not in English. For each such reference, the undersigned has enclosed (i) a translation of the reference; (ii) a copy of a communication from a foreign patent office or International Searching Authority citing the reference, (iii) a copy of a reference which appears to be an English-language counterpart, or (iv) an English-language abstract for the reference prepared by a third party. Applicant has not verified that the translation, English-language counterpart or third-party abstract is an accurate representation of the teachings of the non-English reference, though, and reserves the right to demonstrate otherwise.

- ☐ All cited references
- ☐ References marked by ampersands
- ☐ The following:

3. Effect of Information Disclosure Statement (37 C.F.R. § 1.97(h))

This Information Disclosure Statement is not to be construed as a representation that: (i) a search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the cited information is, or is considered to be, material to patentability. In addition, applicant does not admit that any enclosed item of information constitutes prior art to the subject invention and specifically reserves the right to demonstrate that any such reference is not prior art.

4. Fee Payment

No fees are believed due because this Information Disclosure Statement is being filed before the mailing date of the first Office Action.

☐ Applicant further submits that no fee is due in light of the following certification under 37 C.F.R. § 1.97(e) (check only one):

- ☐ In accordance with 37 C.F.R. § 1.97(e)(1), the undersigned hereby states that each item of information submitted herewith was cited in a communication from a foreign patent office in a counterpart

foreign application not more than three months prior to the filing of this statement; or

☐ In accordance with 37 C.F.R. § 1.97(e)(2), the undersigned hereby states that no item of information submitted herewith was cited in a communication from a foreign patent office in a counterpart foreign application, or, to the knowledge of the person signing the certification after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c), more than three months prior to the filing of this statement.

However, should the Commissioner determine that fees are due in order for this Information Disclosure Statement to be considered, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-2586.

5. Patent Term Adjustment (37 C.F.R. § 1.704(d))

☐ The undersigned states that each item of information submitted herewith was cited in a communication from a foreign patent office in a counterpart application and that this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty days prior to the filing of this statement. 37 C.F.R. § 1.704(d).

Respectfully submitted,
Perkins Coie LLP

Date: May 16, 2012

/Patrick D. Morris/
Patrick D. Morris, Ph.D.
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/417,137	03/09/2012	Bruce SCHARSCHMIDT	79532.8003.US02

CONFIRMATION NO. 6423

34055
PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE, WA 98111-1208

POA ACCEPTANCE LETTER

OC000000054440008

Date Mailed: 05/25/2012

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/16/2012.

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

/rsantos/

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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/417,137

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	95		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	310		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	125		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	27 minus 20 =	* 7	x 30 =	210	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x 125 =	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))				225			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	965		TOTAL	

APPLICATION AS AMENDED - PART II

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

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

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

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/417,137	03/09/2012	1629	1030	79532.8003.US02	12	3

CONFIRMATION NO. 6423

UPDATED FILING RECEIPT

34055
PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE, WA 98111-1208

OC0000000054439983

Date Mailed: 05/25/2012

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**

Applicant(s)

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

Power of Attorney: The patent practitioners associated with Customer Number 34055

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/564,668 11/29/2011
and claims benefit of 61/542,100 09/30/2011

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 03/22/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/417,137**

Projected Publication Date: 04/04/2013

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **

Title

METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

Preliminary Class

514

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 (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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

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

NOT GRANTED

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

79532-8003.WO00
PDA/CDK

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PATENT DOCKETING

JUN 25 2012

PERKINS COIE LLP

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: PATRICK MORRIS
PERKINS COIE LLP
P.O. BOX 1208
SEATTLE, WA 98111-1208

DOCKETED TO CPI
☑ Deadline 1/30/13
☐ Follow up
☐ Previously
☐ Abandoned
☐ Transferred 7/30/13
☐ Dedocketed

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 795328003WO	Date of mailing *(day/month/year)* 20 JUN 2012 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2012/028620	International filing date *(day/month/year)* 09 March 2012
Applicant SCHARSCHMIDT, BRUCE	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 795328003WO	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2012/028620	International filing date *(day/month/year)* 09 March 2012	(Earliest) Priority Date *(day/month/year)* 30 September 2011
Applicant SCHARSCHMIDT, BRUCE		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the language, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
   b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. 2
      ☒ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/028620

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 49/00 (2012.01)
USPC - 424/9.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61B 5/00; A61K 31/192; A61K 49/00; A61P 13/00 (2012.01)
USPC - 424/9.2; 514/568; 600/322, 341

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, Google Patent, Google, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2010/0008859 A1 (SCHARSCHMIDT) 14 January 2010 (14.01.2010) entire document	1-7, 9-12 --- 8
Y	ENNS et al., Survival after Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders, N Engl J Med 356; 22, 31 May 2007. entire document.	8
A	US 6,219,567 B1 (EGGERS et al) 17 April 2001 (17.04.2001) entire document	1-12
A	LEE et al., Phase 2 Comparison of A Novel Ammonia Scavenging Agent with Sodium Phenylbutyrate in Patients with Urea Cycle Disorders: Safety, Pharmacokinetics, and Ammonia Control. Mol. Genet Metab. 100(3) July 2010 entire document	1-12
A	LICHTER-KONECKI et al., Ammonia Control with Urea Cycle Disorders (UCDs); Phase 2 comparison of sodium phenylbutyrate and glycerol phynylbutyrate. Mol. Genet. Metab. 103 5 May 2011. entire document	1-12

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 June 2012	20 JUN 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: PATRICK MORRIS
PERKINS COIE LLP
P.O. BOX 1208
SEATTLE, WA 98111-1208

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	20 JUN 2012
Applicant's or agent's file reference 795328003WO	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2012/028620	09 March 2012	30 September 2011

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 49/00 (2012.01)
USPC - 424/9.2

Applicant SCHARSCHMIDT, BRUCE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	04 June 2012	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/028620

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/028620

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	8	YES
	Claims	1-7, 9-12	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-7 and 9-12 lack novelty under PCT Article 33(2) as being anticipated by Scharschmidt et al. (hereafter Scharschmidt).

Regarding claim 1, Scharschmidt discloses the method (method, Para. [0039]) for determining whether to increase a dosage of a nitrogen scavenging drug in a subject (adjusting the schedule and dose of orally administered nitrogen scavenging drugs, Para. [0020]) currently receiving the nitrogen scavenging drug (method involves administering an initial dosage of the prodrug that is selected based on the patient's current dosage (already receiving a drug), Para. [0044]) comprising:

a) measuring a fasting blood ammonia level (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject (subjects, Para. [0213]);
b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level ((comparing fasting with) normal upper limit for venous (blood) ammonia, Para. [0201], plasma upper limit of normal, Para. [0094]) to determine whether to increase the dosage of a nitrogen scavenging drug (determining and adjusting the dose of an ammonia scavenging drug, Para. [0041]), wherein the dosage needs to be increased if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level (if the ammonia control is inadequate, the dosage of the nitrogen scavenging drug can be increased, Para. [0083]; ammonia value after HPN-100 treatment (26.1 umol/L) was within the normal range and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximatley 26 to 35 umol/L; half the upper limit of normal is about 13 to 17.5 umol/L which is greater than 26. 1 umol/L), Para. [0201]).

Regarding claim 2, Scharschmidt discloses the method (method, Para. [0039]) for determining whether to administer a nitrogen scavenging drug (adjusting the schedule and dose of orally administered nitrogen scavenging drugs, Para. [0020]) to a subject having a nitrogen retention disorder (retention states including urea cycle disorders and liver disease, Para. [0064]) comprising:

a) measuring a fasting blood ammonia level for the subject (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject (subjects, Para. [0213]); and

b) comparing the fasting blood ammonia level to the upper limit of normal for blood ((comparing) normal upper limit for venous (blood) ammonia, Para. [0201], plasma upper limit of normal, Para. [0094]) ammonia levels to determine whether to administer a nitrogen scavenging drug to the subject (determining the dose of an ammonia scavenging drug to be administered, Para. [0041]), wherein a nitrogen scavenging drug needs to be administered to the subject if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level (adjusting the initial dosage of the new drug based upon ammonia control, Para. [0099]; (ammonia value after HPN-100 treatment (26.1 umol/L) was within the normal range and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximatley 26 to 35 umol/L; half the upper limit of normal is about 13 to 17.5 umol/L which is greater than 26.1 umol/L), Para. [0201]).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/028620

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Regarding claim 3, Scharschmidt discloses the method (method, Para. [0039]) of treating a subject with a nitrogen retention disorder (dosing schedule and dose adjustments necessary for treatment of nitrogen retention states including urea cycle disorders and liver disease complicated by hepatic encephalopathy, Para. [0064]) who has previously been administered a nitrogen scavenging drug (method involves administering an initial dosage of the prodrug that is selected based on the patient's current dosage (already receiving a drug), Para. [0044]) comprising:

a) measuring a fasting blood ammonia level (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject (subjects, Para. [0213]); and
b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level and administering an increased dosage of the nitrogen scavenging drug (If the ammonia control is inadequate, the dosage of the nitrogen scavenging drug can be increased, Para. [0083]) if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level (ammonia value after HPN-100 (26.1 umol/L) was within the normal range of 26 to 35 umol/L and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximatley 26 to 35 umol/L; half the upper limit of normal is about 13 to 17.5 umol/L which is greater than 26.1 umol/L), Para. [0201]).

Regarding claim 4, Scharschmidt discloses the method of claim 1. Scharschmidt discloses further comprising: c) administering an increased dosage of the nitrogen scavenging drug if the need exists (treatment with an ammonia scavenging agent as described in this invention is determined clinically if the subject is in need of such treatment. This clinical determination would be based upon a variety of factors (e.g. signs and symptoms of hepatic encephalopathy in patients with cirrhosis, elevated blood ammonia levels), Para. [0221]);

Regarding claim 5, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses wherein the nitrogen retention disorder is selected from the group consisting of a urea cycle disorders and hepatic encephalopathy (urea cycle disorder, Para. [0221], hepatic encephalopathy, Para. [0041]).

Regarding claim 6, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses wherein the nitrogen scavenging drug is a PAA prodrug (prodrugs of PAA, Para. [0217]).

Regarding claim 7, Scharschmidt discloses the method of claim 6. Scharschmidt discloses wherein the PAA prodrug is selected from the group consisting of glyceryl tri-[4-phenylbutyrate] (HPN-100), phenylbutyric acid (PBA), sodium PBA (NaPEA), and a combination of two or more of HPN-100, PBA, and NaPBA (HPN-100, Para. [0020]).

Regarding claim 9, Scharschmidt discloses the method of claim 3 or 4. Scharschmidt discloses wherein administering an increased dosage of the nitrogen scavenging drug produces a normal average daily ammonia level in the subject (administering the effective dosage of HPN-100 (effective dose may require increasing or decreasing the drug) to the patient preferably produces a normal plasma ammonia level in the patient, Para. [0142]); nitrogen scavenging drug may need to be increased, Para. [0083]).

Regarding claim 10, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses further comprising the step of determining an upper limit of normal for blood ammonia level for the subject prior to step (b) (monitoring the effect of the initial dosage of HPN-100 consists essentially of determining the patient's urinary phenylacetyl glutamine (PAGN) output and/or total urinary nitrogen. Administering the effective dose of HPN-100 to the patient produces a normal plasma ammonia level. Plasma ammonia in the patient can be a level of about 35 or about 40 umol/L (determining the upper limit of normal for the subject via urinary excretion of PAGN prior to step b), Para. [0142]); the normal upper limit for venous (blood) ammonia varied among the study sites from 26 to 35 umol/L, Para. [0201]).

Regarding claim 11, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses wherein the upper limit of normal blood ammonia level is 35 umol/L (upper limit of normal for subjects is between 26 to 35 umol/L, Para. [0094]).

Regarding claim 12, Scharschmidt discloses the method of claim 6. Scharschmidt discloses further comprising:
c) measuring urinary PAGN excretion (measuring PAGN excretion, Para. [0096]); and
e) determining an effective dosage of the PAA (effective dose, Para. [0140]), prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60-75% (determining an amount of the PAA prodrug needed to mobilize the target amount of urinary PAGN based on about 60% to about 75% conversion of the PAA prodrug into urinary PAGN, Para. [0148]).

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/028620

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Claim 8 lacks an inventive step under PCT Article 33(3) as being obvious over Scharschmidt et al.(hereafter Scharschmidt) in view of Ennis et al. (hereafter Ennis).

Regarding claim 8, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt fails to explicitly disclose wherein the nitrogen scavenging drug is sodium benzoate. Ennis is in the field of treating urea cycle disorders with phenylacetate and benzoate and teaches the use of sodium benzoate to treat patients with ammonia disorders (sodium benzoate therapy in patients, Pg. 1, Lns.1-16). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the therapeutic drug sodium benzoate as taught by Ennis with the method of Scharschmidt. The motivation would have been to lower plasma ammonium levels and improve the survival of patients with lethal urea-cycle enzyme defects (Ennis, lower plasma ammonium levels and improve survival in small cohorts of patients with historically lethal urea-cycle enzyme defects, Pg. 1, Lns. 1-16).

Claims 1-12 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Electronic Acknowledgement Receipt

EFS ID:	13131186
Application Number:	13417137
International Application Number:	
Confirmation Number:	6423
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Patrick D. Morris/Colleen Kirchner
Filer Authorized By:	Patrick D. Morris
Attorney Docket Number:	79532.8003.US02
Receipt Date:	28-JUN-2012
Filing Date:	09-MAR-2012
Time Stamp:	14:44:18
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	Enns.pdf	217222 5362f6c61e8308894e286bcc6da28b2583c1d937	no	11
Warnings:					
Information:					

2	Non Patent Literature	ISR_WO.pdf	398953 5763d426b44557fd539b95e2fa5b181f1f0f99e19	no	8
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	Supplemental_IDS_8003US02.pdf	612460 ed1fc1852741f6b2c315e54071bf396fcccb9f9f	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	1228635		

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

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

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

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

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13417137
Filing Date	2012-03-09
First Named Inventor	Bruce Scharschmidt
Art Unit	1629
Examiner Name	To be assigned
Attorney Docket Number	79532.8003.US02

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6219567	B1	2001-04-17	EGGERS et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20100008859	A1	2010-01-14	SCHARSCHMIDT	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	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, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13417137
	Filing Date	2012-03-09
	First Named Inventor	Bruce Scharschmidt
	Art Unit	1629
	Examiner Name	To be assigned
	Attorney Docket Number	79532.8003.US02

	1	ENNS, G. M., et al., "Survival After Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders," N. Eng. J. Med. 356:2282-2292 (2007).	☐
	2	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion dated June 4, 2012 for PCT/US2012/028620.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13417137
	Filing Date	2012-03-09
	First Named Inventor	Bruce Scharschmidt
	Art Unit	1629
	Examiner Name	To be assigned
	Attorney Docket Number	79532.8003.US02

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Patrick D. Morris/	Date (YYYY-MM-DD)	2012-06-28
Name/Print	Patrick D. Morris	Registration Number	53,351

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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CONFIRMATION NO. 6423

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/417,137	03/09/2012 RULE	514	1629	79532.8003.US02

APPLICANTS

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

**** CONTINUING DATA ***************************

This appln claims benefit of 61/564,668 11/29/2011
and claims benefit of 61/542,100 09/30/2011

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

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Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /SAVITHA M RAO/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	3	12	3

ADDRESS

PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE, WA 98111-1208
UNITED STATES

TITLE

METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

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                  CSA Databases Allows More Efficient Searching on STN
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reclassification data for the fourth quarter of 2012.

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

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

=> d l2 ibib ab

L2   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:        2010:708850  CAPLUS
DOCUMENT NUMBER:         154:477123
TITLE:                   Phase 2 comparison of a novel ammonia scavenging agent
                         with sodium phenylbutyrate in patients with urea cycle
                         disorders: Safety, pharmacokinetics and ammonia
                         control
AUTHOR(S):               Lee, Brendan; Rhead, William; Diaz, George A.;
                         Scharschmidt, Bruce F.; Mian, Asad; Shchelochkov,
                         Oleg; Marier, J. F.; Beliveau, Martin; Mauney, Joseph;
                         Dickinson, Klara; Martinez, Antonia; Gargosky,
                         Sharron; Mokhtarani, Masoud; Berry, Susan A.
CORPORATE SOURCE:        Baylor College of Medicine, Houston, TX, R814, USA
SOURCE:                  Molecular Genetics and Metabolism (2010), 100(3),
                         221-228
                         CODEN: MGMEFF; ISSN: 1096-7192
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Glycerol phenylbutyrate (glyceryl tri (4-phenylbutyrate)) (GPB) is being
     studied as an alternative to sodium phenylbutyrate (NaPBA) for the
     treatment of urea cycle disorders (UCDs).  This phase 2 study explored the
     hypothesis that GPB offers similar safety and ammonia control as NaPBA,
     which is currently approved as adjunctive therapy in the chronic
     management of UCDs, and examined correlates of 24-h blood ammonia.  Methods:
     An open-label, fixed sequence switch-over study was conducted in adult UCD
     patients taking maintenance NaPBA.  Blood ammonia and blood and urine
     metabolites were compared after 7 days (steady state) of TID dosing on
     either drug, both dosed to deliver the same amount of phenylbutyric acid
     (PBA).  Results: Ten subjects completed the study.  Adverse events were
     comparable for the two drugs; 2 subjects experienced hyperammonemic events
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     on NaPBA while none occurred on GPB.  Ammonia values on GPB were
     .apprx.30% lower than on NaPBA (time-normalized AUC = 26.2 vs. 38.4
     μmol/L; Cmax = 56.3 vs. 79.1 μmol/L; not statistically significant),
     and GPB achieved non-inferiority to NaPBA with respect to ammonia
     (time-normalized AUC) by post hoc anal.  Systemic exposure (AUC0-24) to
     PBA on GPB was 27% lower than on NaPBA (540 vs. 739 μg h/mL), whereas
     exposure to phenylacetic acid (PAA) (575 vs. 596 μg h/mL) and
     phenylacetylglutamine (PAGN) (1098 vs. 1133 μg h/mL) were similar.
     Urinary PAGN excretion accounted for .apprx.54% of PBA administered for
     both NaPBA and GPB; other metabolites accounted for <1%.  Intact GPB was
     generally undetectable in blood and urine.  Blood ammonia correlated
     strongly and inversely with urinary PAGN (r = -0.82; p < 0.0001) but
     weakly or not at all with blood metabolite levels.  Conclusions: Safety
     and ammonia control with GPB appear at least equal to NaPBA.  Urinary
     PAGN, which is stoichiometrically related to nitrogen scavenging, may
     be a useful biomarker for both dose selection and adjustment for optimal
     control of venous ammonia.
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     FILE 'CAPLUS' ENTERED AT 07:19:34 ON 16 NOV 2012
L1           32 S "NITROGEN SCAVENGING"
L2            1 S L1 AND PAA

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

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

=> s l1 and phenylbutyric
             0 "NITROGEN"
             0 "SCAVENGING"
             0 "NITROGEN SCAVENGING"
                 ("NITROGEN"(W)"SCAVENGING")
             0 PHENYLBUTYRIC
L4           0 L1 AND PHENYLBUTYRIC
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=> s nitrogen
L5          0 NITROGEN

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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     1.62      15.07

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FILE LAST UPDATED: 15 Nov 2012  (20121115/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  September 2012
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=> s nitrogen
        951198 NITROGEN
          4883 NITROGENS
L6      954619 NITROGEN
                 (NITROGEN OR NITROGENS)

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

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

=> d l8 ibib ab
```

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:708850 CAPLUS
DOCUMENT NUMBER: 154:477123
TITLE: Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: Safety, pharmacokinetics and ammonia control
AUTHOR(S): Lee, Brendan; Rhead, William; Diaz, George A.; Scharschmidt, Bruce F.; Mian, Asad; Shchelochkov, Oleg; Marier, J. F.; Beliveau, Martin; Mauney, Joseph; Dickinson, Klara; Martinez, Antonia; Gargosky, Sharron; Mokhtarani, Masoud; Berry, Susan A.
CORPORATE SOURCE: Baylor College of Medicine, Houston, TX, R814, USA
SOURCE: Molecular Genetics and Metabolism (2010), 100(3), 221-228
CODEN: MGMEFF; ISSN: 1096-7192
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glycerol phenylbutyrate (glyceryl tri (4-phenylbutyrate)) (GPB) is being studied as an alternative to sodium phenylbutyrate (NaPBA) for the treatment of urea cycle disorders (UCDs). This phase 2 study explored the hypothesis that GPB offers similar safety and ammonia control as NaPBA, which is currently approved as adjunctive therapy in the chronic management of UCDs, and examined correlates of 24-h blood ammonia. Methods: An open-label, fixed sequence switch-over study was conducted in adult UCD patients taking maintenance NaPBA. Blood ammonia and blood and urine metabolites were compared after 7 days (steady state) of TID dosing on either drug, both dosed to deliver the same amount of phenylbutyric acid (PBA). Results: Ten subjects completed the study. Adverse events were comparable for the two drugs; 2 subjects experienced hyperammonemic events on NaPBA while none occurred on GPB. Ammonia values on GPB were .apprx.30% lower than on NaPBA (time-normalized AUC = 26.2 vs. 38.4 μmol/L; Cmax = 56.3 vs. 79.1 μmol/L; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time-normalized AUC) by post hoc anal. Systemic exposure (AUC0-24) to PBA on GPB was 27% lower than on NaPBA (540 vs. 739 μg h/mL), whereas exposure to phenylacetic acid (PAA) (575 vs. 596 μg h/mL) and phenylacetylglutamine (PAGN) (1098 vs. 1133 μg h/mL) were similar. Urinary PAGN excretion accounted for .apprx.54% of PBA administered for both NaPBA and GPB; other metabolites accounted for <1%. Intact GPB was generally undetectable in blood and urine. Blood ammonia correlated strongly and inversely with urinary PAGN ($r = -0.82$; $p < 0.0001$) but weakly or not at all with blood metabolite levels. Conclusions: Safety and ammonia control with GPB appear at least equal to NaPBA. Urinary PAGN, which is stoichiometrically related to nitrogen scavenging, may be a useful biomarker for both dose selection and adjustment for optimal control of venous ammonia.
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REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s PAA prodrug
10799 PAA
573 PAAS
11191 PAA
(PAA OR PAAS)
17954 PRODRUG
20950 PRODRUGS

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        27897 PRODRUG
                (PRODRUG OR PRODRUGS)
L9          0 PAA PRODRUG
                (PAA(W)PRODRUG)

=> s PAA
        10799 PAA
          573 PAAS
L10     11191 PAA
                (PAA OR PAAS)

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

=> d l11 1-9 ibib ab

L11  ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:        2012:1197939  CAPLUS
DOCUMENT NUMBER:         157:426609
TITLE:                   Determination of phenylbutyric acid and its metabolite
                         phenylacetic acid in different tissues of mouse by
                         liquid chromatography with tandem mass spectrometry
                         and its application in drug tissue distribution
AUTHOR(S):               Marahatta, Anu; Bhandary, Bidur; Lee, Mi-Rin; Kim,
                         Do-Sung; Lee, Yong Chul; Kim, So-Ri; Kim, Hyung-Ryong;
                         Chae, Han-Jung
CORPORATE SOURCE:        Department of Pharmacology, School of Medicine,
                         Chonbuk National University, Jeonju, 560-182, S. Korea
SOURCE:                  Journal of Chromatography, B: Analytical Technologies
                         in the Biomedical and Life Sciences (2012), 903,
                         118-125
                         CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal; (online computer file)
LANGUAGE:                English
AB   Endoplasmic reticulum (ER) stress is associated with various human diseases.
     Phenylbutyric acid (PBA) is a well-known chemical chaperone that regulates ER
     stress.  The main objective of this study was to develop a simple, rapid,
     and sensitive method for the simultaneous determination of phenylbutyric acid
and
     its metabolite, phenylacetic acid (PAA).  A LC-MS/MS anal. using neg.
     electrospray ionization was used.  Samples were analyzed by multiple
     reaction monitoring (MRM) in 15 min of total run time, using d11-PBA and
     d7-PAA as internal stds.  The limit of quantification was 1 μg/g for
     tissue and 0.8 μg/mL for plasma.  Recoveries for plasma and tissues
     were higher than 81% for both PBA and PAA.  The inter-day and intra-day
     accuracy and precision were within ±15%.  We then further successfully
     validated this method by applying it to determine the tissue distribution of
     PBA and its metabolite PAA after i.p. injection of PBA at a dose of 500
     mg/kg in mice.  The maximum concns. of PBA and PAA in plasma and tissues
     were seen at 15 min and 45 min, resp.  The PBA plasma concentration was 15-fold
     higher than the concentration in the kidney, whereas the PAA plasma
concentration was
     6-fold higher than the concentration in the liver.  The area under the curve
     decreased in the order of plasma > kidney > liver > heart > muscle > lung
     for PBA and plasma > liver > kidney > heart > muscle > lung for PAA.
     The tissue to plasma ratio ranged from 0.007 to 0.063 for PBA and 0.016 to
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0.109 for PAA. In summary, the LC-ESI-MS method developed in this study is simple, sensitive and reliable.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1275522 CAPLUS
DOCUMENT NUMBER: 156:626560
TITLE: Macromolecular prodrugs based on synthetic polyaminoacids: drug delivery and drug targeting in antitumor therapy
AUTHOR(S): Cavallaro, Gennara; Pitarresi, Giovanna; Giammona, Gaetano
CORPORATE SOURCE: Dipartimento di Chimica e Tecnologie Farmaceutiche, Universita degli Studi di Palermo, Palermo, 90123, Italy
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) (2011), 11(18), 2382-2389
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. In the last twenty years a depth study on potential pharmaceutical applications of synthetic polymers at protein-like structure as carrier for macromol. prodrug production has been performed in academia and in industry. In particular α,β-poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA), α,β-polyaspartylhydrazide (PAHy), poly(glutamic acid) (PGA), poly(aspartic acid) (PAA) and polylysine (PLL) have been extensively studied in this field. In the present review, the use of PHEA, PAHy, PGA as starting materials to prepare macromol. prodrugs is reported and drug delivery and targeting aspects have been considered.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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

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

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

azimino-containing medicine mol. via click reaction, reacting the alkynyl with azido-ended polyethyleneglycol monomethyl ether via click reaction. The method is highly effective, safe and simple.

L11 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1063363 CAPLUS
DOCUMENT NUMBER: 153:626843
TITLE: Nanomicelle with long-term circulation and enhanced stability of camptothecin based on mPEGylated α,β-poly (L-aspartic acid)-camptothecin conjugate
AUTHOR(S): Zhang, Weilu; Huang, Jin; Fan, Naiqian; Yu, Jiahui; Liu, Yongbiao; Liu, Shiyuan; Wang, Daxin; Li, Yaping
CORPORATE SOURCE: Institutes for Advanced Interdisciplinary Research, East China Normal University, Shanghai, 200062, Peop. Rep. China
SOURCE: Colloids and Surfaces, B: Biointerfaces (2010), 81(1), 297-303
CODEN: CSBBEQ; ISSN: 0927-7765
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 153:626843
AB To enhance the stability and long-term circulation of camptothecin (CPT), mPEGylated α,β-poly (L-aspartic acid)-CPT conjugates were synthesized, and used to fabricate nanomicelle. Firstly, α,β-poly (L-aspartic acid) derivative (PAA-der) containing alkyne groups was synthesized via the ring-opening of PSI with propargyl amine. Then, azide-functionalized CPT derivs. (CPT-N3) and azide-terminated poly (ethylene glycol) Me ether (mPEG-N3) were conjugated with PAA-der by click cycloaddn. to give mPEG-graft-PAA-CPT conjugates. The formation of mPEG-graft-PAA-CPT nanomicelles was confirmed by fluorescence spectrophotoscopy and particle size measurements. It was found that all the nanomicelles showed spherical shapes with size about 178 nm. MPEG-graft-PAA-CPT nanomicelles showed good storage stability, even incubation at 37° for 60 days, and improved the stability of CPT lactone form in aqueous media. A steady release rate of CPT was kept for 72 h, suggested the great potential of mPEG-graft-PAA-CPT nanomicelles as polymer prodrug of CPT.
OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2005:622439 CAPLUS
DOCUMENT NUMBER: 143:278873
TITLE: Mechanism of poly(acrylic acid) acceleration of antithrombin inhibition of thrombin: implications for design of novel heparin mimics
AUTHOR(S): Monien, Bernhard H.; Cheang, Kai I.; Desai, Umesh R.
CORPORATE SOURCE: Departments of Medicinal Chemistry and Pharmacy and Institute for Structural Biology and Drug Discovery, Virginia Commonwealth University, Richmond, VA, 23298, USA
SOURCE: Journal of Medicinal Chemistry (2005), 48(16), 5360-5368
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The bridging mechanism of antithrombin inhibition of thrombin is a dominant mechanism contributing a massive .apprx.2500-fold acceleration in the reaction rate and is also a key reason for the clin. usage of heparin. Our recent study of the antithrombin-activating properties of a carboxylic acid-based polymer, poly(acrylic acid) (PAA), demonstrated a surprisingly high acceleration in thrombin inhibition (Monien, B. H.; Desai, U. R. J. Med. Chemical 2005, 48, 1269). To better understand this interesting phenomenon, we have studied the mechanism of PAA-dependent acceleration in antithrombin inhibition of thrombin. Competitive binding studies with low-affinity heparin and a heparin tetrasaccharide suggest that PAA binds antithrombin in both the pentasaccharide- and the extended heparin-binding sites, and these results are corroborated by mol. modeling. The salt-dependence of the KD of the PAA-antithrombin interaction shows the formation of five ionic interactions. In contrast, the contribution of nonionic forces is miniscule, resulting in an interaction that is significantly weaker than that observed for heparins. A bell-shaped profile of the observed rate constant for antithrombin inhibition of thrombin as a function of PAA concentration was observed, suggesting that inhibition proceeds through the "bridging" mechanism. The knowledge gained in this mechanistic study highlights important rules for the rational design of orally available heparin mimics.

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

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

L11 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2000:890604 CAPLUS

DOCUMENT NUMBER: 134:242530

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

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

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

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

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

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

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

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 1997:5450 CAPLUS
TITLE: Patent evaluation anti-infectives Phosphonic acid prodrugs with improved antiviral activity
CORPORATE SOURCE: Univ. California, USA
SOURCE: Expert Opinion on Therapeutic Patents (1996), 6(12), 1331-1333
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This patent discloses lipid derivs. as prodrugs for antiviral agents. It relates particularly to lipid prodrugs of phosphonic acids and their use in the treatment of viral infections. The invention claims a series of improved prodrugs of phosphonoformate (PFA), phosphonoacetate (PAA) and their analogs, with increased in vitro antiviral activity over the parent compds. against human cytomegalovirus (HCMV), herpes simplex virus (HSV) and human immunodeficiency virus (HIV).

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

L11 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN

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ACCESSION NUMBER:         1985:67342  CAPLUS
DOCUMENT NUMBER:          102:67342
ORIGINAL REFERENCE NO.:   102:10499a,10502a
TITLE:                    Physicochemical and antitumor characteristics of some
                          polyamino acid prodrugs of mitomycin C
AUTHOR(S):                Roos, C. F.; Matsumoto, Satoshi; Takakura, Yoshinobu;
                          Hashida, Mitsuru; Sezaki, Hitoshi
CORPORATE SOURCE:         Fac. Pharm. Sci., Kyoto Univ., Kyoto, 606, Japan
SOURCE:                   International Journal of Pharmaceutics (1984), 22(1),
                          75-87
                          CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Mitomycin C (MMC) conjugates with the polyamino acids: poly-L-glutamic
     acid (PGA; mol. weight 11,000 and 60,000), poly-L-aspartic acid (PAA; mol.
     weight 14,000) and poly-L-lysine (PLY; mol. weight 13,000) were synthesized to
     obtain more information about the application of polyamino acids as high
     mol. weight carriers.  Some physicochem. and antitumor characteristics of
     these conjugates were investigated.  Gel filtration confirmed covalent
     binding and provided information about the mol. sizes.  The release rates
     of MMC  [50-07-7] from conjugates were determined in vitro.  The PAA and PGA
     (mol. weight 11,000) conjugates acted as neg. charged mols. in their
     interaction with ion exchangers.  The PLY conjugate showed a pos. charge
     and was able to bind to Ehrlich ascites carcinoma cells in vitro.  The
     effects of 1 h exposure of mouse L1210 leukemia cells to the conjugates
     were evaluated using cell culture system.  In this experiment, only the PLY
     conjugate showed better effects than MMC.  Continuous exposure to the
     conjugates showed a similar effect to MMC.  In vivo, less toxicity was
     found for the conjugates than for MMC.  The PGA (mol. weight 11,000) and PLY
     conjugates showed slightly higher effects against P388 leukemia than MMC,
     while no toxic doses were reached.
OS.CITING REF COUNT:      14    THERE ARE 14 CAPLUS RECORDS THAT CITE THIS
                                RECORD (14 CITINGS)


=> d his

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

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

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

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

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	0	"13417137".rlan. or ("13".src. and "417137".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 13:46
S2	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:46
S3	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:46
S4	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:56
S5	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:56
S6	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:56
S7	18	("20040229948" | "20060135612" | "4284647" | "6083984" | "20080119554" | "6219567" | "20100008859" | "6050510" | "5968979" | "20100008859" | "6219567").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:57
S8	0	S1 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S9	8	S7 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S10	2	S9 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S11	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:12
S12	4	S11 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:12
S13	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 14:13
S14	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO;	OR	OFF	2012/11/15 14:13

			DERWENT; IBM_TDB			
S15	18	("4284647" | "6083984" | "6050510" | "6219567" | "20040229948" | "20080119554" | "20060135612" | "5968979" | "20100008859").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/16 07:11
S16	2	S15 and "nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/16 07:11
S17	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2012/11/16 07:12
S18	9	((Saul) near2 (Brusilow)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/16 07:13

11/ 16/ 2012 8:21:39 AM
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
Form PTO-1449 (Modified)
(Use several sheets if necessary)

Sheet 1 of 10

COMPLETE IF KNOWN	
Application Number	13/417,137
Confirmation Number	6423
Filing Date	2012-03-09
First Named Inventor	Bruce SCHARSCHMIDT
Group Art Unit	1629
Examiner Name	To be assigned
Attorney Docket No.	79532.8003.US02

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	U.S. Patent or Application NUMBER	Kind Code (if known)	Name of Patentee or Inventor of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Figures Appear
	A1	2004/0229948	A1	SUMMAR et al.	11/18/2004	
	A2	2006/0135612	A1	FERRANTE	06/22/2006	
	A3	2008/119554	A1	JALAN et al.	05/22/2008	
	A4	4,284,647		BRUSILOW et al.	08/18/1981	
	A5	5,968,979		BRUSILOW	10/19/1999	
	A6	6,050,510	A	BONNEWITZ	05/09/2000	
	A7	6,083,984		BRUSILOW	07/04/2000	

FOREIGN PATENT DOCUMENTS

Examiner Initial	Cite No.	Foreign Patent or Application Office	NUMBER	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Figures Appear	T
	B1	WO	2005/053607	A1	MEDICIS PHARMACEUTICAL CORP.	06/16/2005		
	B2	WO	2006/056794		UCL BUSINESS PLC	06/01/2006		
	B3	WO	2009/087474		AKTHELIA PHARMACEUTICALS	07/16/2009		
	B4	WO	2009/134460	A1	HYPERION THERAPEUTICS	11/05/2009		
	B5	WO	2010/0250303	A1	HYPERION THERAPEUTICS	03/04/2010		

OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	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
	C1	AMBROSE, A.M. et al. (1933). "Further Studies on the Detoxification of Phenylacetic Acid," J. Bio. Chem. 101:669-675.	
	C2	BATSHAW, M.L. et al. (December 1980). "Treatment of Hyperammonemic Coma Caused by Inborn Errors of Urea Synthesis," J. Pediatr. 97(6):893-900.	

EXAMINER	DATE CONSIDERED
/Savitha Rao/	11/15/2012

*EXAMINER: Initial if reference considered, whether or not criteria 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 application(s).

79532-8003.US02/LEGAL 23682286.1

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
Form PTO-1449 (Modified)
(Use several sheets if necessary)

Sheet	2	of	10

COMPLETE IF KNOWN	
Application Number	13/417,137
Confirmation Number	6423
Filing Date	2012-03-09
First Named Inventor	Bruce SCHARSCHMIDT
Group Art Unit	1629
Examiner Name	To be assigned
Attorney Docket No.	79532.8003.US02

OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	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
	C3	BATSHAW, M.L. et al. (August 1981). "New Approaches to the Diagnosis and Treatment of Inborn Errors of Urea Synthesis," Pediatrics 68(2):290-297.	
	C4	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.	
	C5	BATSHAW, M.L. (1984). "Hyperammonemia," in Current Problems in Pediatrics, Lockhart, J.D. ed.: Year Book Medical Publishers, pp. 2-69.	
	C6	BERRY, G. T., et al., "Long-Term Management of Patients with Urea Cycle Disorders," J. Pediatrics (2001) 138:S56-S61.	
	C7	BRUSILOW, S., et al., "Amino Acid Acylation: A Mechanism of Nitrogen Excretion in Inborn Errors of Urea Synthesis," Science 207:659-661 (1980).	
	C8	BRUSILOW, S. W., et al., "Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion," Pediatr. Res. 29:147-150 (1991).	
	C9	BRUSILOW, S.w. et al. (September 1,1979). "New Pathways of Nitrogen Excretion in Inborn Errors of Urea Synthesis," Lancet 2(8140):452- 454.	
	C10	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.	
	C11	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.	
	C12	BRUSILOW, S.w. 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.	

EXAMINER	DATE CONSIDERED
/Savitha Rao/	11/15/2012

*EXAMINER: Initial if reference considered, whether or not criteria 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 application(s).

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
Form PTO-1449 (Modified)
(Use several sheets if necessary)

Sheet	3	of	10

COMPLETE IF KNOWN	
Application Number	13/417,137
Confirmation Number	6423
Filing Date	2012-03-09
First Named Inventor	Bruce SCHARSCHMIDT
Group Art Unit	1629
Examiner Name	To be assigned
Attorney Docket No.	79532.8003.US02

OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	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
	C13	BRUSILOW, S.W. et al. (1995). "Urea Cycle Enzymes," Chapter 32 in The Metabolic and Molecular bases of Inherited Diseases, Scriver, C.R. et al. eds., McGraw-Hill, Inc. New York, New York, pp.1187-1232.	
	C14	BRUSILOW, S.W., et al. (1996)." Urea Cycle Disorders: Diagnosis, Pathophysiology, and Therapy," Adv. Pediatr. 43:127-170.	
	C15	BRUSILOW, S.W., et al. (1995). "Urea Cycle Disorders: Clinical Paradigm of Hyperammonemic Enecphalopathy," Progress in Liver Diseases (1995) 12:293-309.	
	C16	BRUSILOW, S. W., et al., "Restoration of Nitrogen Homeostasis in a Man with Ornithine Transcarbamylase Deficiency," J. Metabolism (1993) 42:1336-1339.	
	C17	CALLOWAY, D.H. et al. (1971). "Sweat and Miscellaneous Nitrogen Losses in Human Balance Studies," J. Nutrition 101:775-786.	
	C18	CALLOWAY, D.H. et al. (1971). "Variation in Endogenous Nitrogen Excretion and Dietary Nitrogen Utilization as Determinants of Human Protein Requirements," J. Nutrition 101:205-216.	
	C19	CAMACHO, L.H. et al. (2007, e-pub. October 20,2006). "Phase I Dose Escalation Clinical Trial of Phenyl butyrate Sodium Administered Twice Daily to Patients With Advanced Solid Tumors," Invest. New Drugs 25:131-138.	
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COMPLETE IF KNOWN	
Application Number	13/417,137
Confirmation Number	6423
Filing Date	2012-03-09
First Named Inventor	Bruce SCHARSCHMIDT
Group Art Unit	1629
Examiner Name	To be assigned
Attorney Docket No.	79532.8003.US02

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First Named Inventor	Bruce SCHARSCHMIDT
Group Art Unit	1629
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Application Number	13417137
Filing Date	2012-03-09
First Named Inventor	Bruce Scharschmidt
Art Unit	1629
Examiner Name	To be assigned
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Receipt date: 06/28/2012	Application Number	13417137 13417137 - GAU: 1629
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2012-03-09
	First Named Inventor	Bruce Scharschmidt
(Not for submission under 37 CFR 1.99)	Art Unit	1629
	Examiner Name	To be assigned
	Attorney Docket Number	79532.8003.US02

	1	ENNS, G. M., et al., "Survival After Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders," N. Eng. J. Med. 356:2282-2292 (2007).	☐
	2	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion dated June 4, 2012 for PCT/US2012/028620.	☐

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/417,137	03/09/2012	Bruce SCHARSCHMIDT	79532.8003.US02	6423

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RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
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Office Action Summary	Application No.	Applicant(s)	
	13/417,137	SCHARSCHMIDT ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1629	

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- 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 *09 March 2012*.

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) *1-12* 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) *1-12* 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).

a)☐ All b)☐ Some * c)☐ None of:

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/08) Paper No(s)/Mail Date *05/16/2012, 06/28/2012*.

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

4) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending and have been considered on the merits herein.

Information Disclosure Statement

The information disclosure statement (IDS) dated 05/16/20102 and 06/28/2012 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.

Priority

This application claims benefit of U.S. Provisional Application No. 61/564668, filed on 11/29/2011 and Provisional Application No. 61/542100 filed on 09/30/2011.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Scharschmidt (US 2010/0008859, cited in the IDS dated 06/28/2012))

Scharschmidt discloses the method (method, Para. [0039]) for determining whether to increase a dosage of a nitrogen scavenging drug in a subject (adjusting the schedule and dose of orally administered nitrogen scavenging drugs, Para. [0020]) currently receiving the nitrogen scavenging drug (method involves administering an initial dosage of the prodrug that is selected based on the patient's current dosage (already receiving a drug), Para. [0044]) comprising: a) measuring a fasting blood

ammonia level (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject (subjects, Para. [0213]); b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level ((comparing fasting with) normal upper limit for venous (blood) ammonia, Para. [0201], plasma upper limit of normal, Para. [0094]) to determine whether to increase the dosage of a nitrogen scavenging drug (determining and adjusting the dose of an ammonia scavenging drug, Para. [0041]), wherein the dosage needs to be increased if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level (If the ammonia control is inadequate, the dosage of the nitrogen scavenging drug can be increased, Para. [0083]; ammonia value after HPN-100 treatment (26.1 umol/L) was within the normal range and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximately 26 to 35 umol/L; half the upper limit of normal is about 13 to 17.5 umol/L which is greater than 26.1 umol/L), Para. [0201]).

Regarding claim 2, Scharschmidt discloses the method (method, Para. [0039]) for determining whether to administer a nitrogen scavenging drug by adjusting the schedule and dose of orally administered nitrogen scavenging drugs, Para. [0020]) to a subject having a nitrogen retention disorder (retention states including urea cycle disorders and liver disease, Para. [0064]) comprising: a) measuring a fasting blood ammonia level for the subject (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject (subjects, Para. [0213]); and b) comparing the fasting blood ammonia level to the upper limit of normal for blood ((comparing) normal upper limit for venous (blood) ammonia, Para. [0201], plasma upper limit of normal, Para. [0094]) ammonia levels to determine whether to administer a nitrogen scavenging drug to the subject (determining the dose of an ammonia scavenging drug to be administered, Para. [0041]), wherein a nitrogen scavenging drug needs to be administered to the subject if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level (adjusting the initial dosage of the new drug based upon ammonia control, Para. [0099]; (ammonia value after HPN-100 treatment (26.1 umol/L) was within the normal range and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximately 26 to 35 umol/L; half the upper limit of normal is about 13 to 17.5 umol/L which is greater than 26.1 umol/L), Para. [0201]).

Regarding claim 3, Scharschmidt discloses the method (method, Para. [0039]) of treating a subject with a nitrogen retention disorder (dosing schedule and dose adjustments necessary for treatment of nitrogen retention states including urea cycle disorders and liver disease complicated by hepatic encephalopathy, Para. [0064]) who has previously been administered a nitrogen scavenging drug (method involves administering an initial dosage of the prodrug that is selected based on the patient's current dosage (already receiving a drug), Para. [0044]) comprising: a) measuring a fasting blood ammonia level (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject (subjects, Para. [0213]); and b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level and administering an increased dosage of the nitrogen scavenging drug (If the ammonia control is inadequate, the dosage of the nitrogen scavenging drug can be increased, Para. [0083]) if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level (ammonia value after HPN-100 (26.1 umol/L) was within the normal range of 26 to 35 umol/L and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximately 26 to 35 umol/L; half the upper limit of normal is about 13 to 17.5 umol/L which is greater than 26.1 umol/L), Para. [0201]).

Regarding claim 4, Scharschmidt discloses the method of claim 1. Scharschmidt discloses further comprising: c) administering an increased dosage of the nitrogen scavenging drug if the need exists (treatment with an ammonia scavenging agent as described in this invention is determined clinically if the subject is in need of such treatment. This clinical determination would be based upon a variety of factors (e.g. signs and symptoms of hepatic encephalopathy in patients with cirrhosis, elevated blood ammonia levels), Para. [0221]);

Regarding claim 5, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses wherein the nitrogen retention disorder is selected from the group consisting of a urea cycle disorders and hepatic encephalopathy (urea cycle disorder, Para. [0221], hepatic encephalopathy, Para. [0041]).

Regarding claim 6, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses wherein the nitrogen scavenging drug is a PAA prodrug (prodrugs of PAA, Para. [0217]).

Regarding claim 7, Scharschmidt discloses the method of claim 6. Scharschmidt discloses wherein the PAA prodrug is selected from the group consisting of glyceryl td-[4-phenylbutyrate] (HPN-100), phenylbutyric acid (PBA), sodium PBA (NaPEA), and a combination of two or more of HPN-100, PBA, and NaPBA (HPN-100, Para. [0020]).

Regarding claim 9, Scharschmidt discloses the method of claim 3 or 4. Scharschmidt discloses wherein administering an increased dosage of the nitrogen scavenging drug produces a normal average daily ammonia level in the subject (administering the effective dosage of HPN-100 (effective dose may require increasing or decreasing the drug) to the patient preferably produces a normal plasma ammonia level in the patient, Para. [0142]); nitrogen scavenging drug may need to be increased, Para. [0083]).

Regarding claim 10, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses further comprising the step of determining an upper limit of normal for blood ammonia level for the subject prior to step (b) (monitoring the effect of the initial dosage of HPN-100 consists essentially of determining the patient's urinary phenylacetyl glutamine (PAGN) output and/or total urinary nitrogen. Administering the effective dose of HPN-100 to the patient produces a normal plasma ammonia level. Plasma ammonia in the patient can be a level of about 35 or about 40 umol/L (determining the upper limit of normal for the subject via urinary excretion of PAGN prior to step b), Para. [0142]); the normal upper limit for venous (blood) ammonia varied among the study sites from 26 to 35 umol/L, Para. [0201]).

Regarding claim 11, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses wherein the upper limit of normal blood ammonia level is 35 umol/L (upper limit of normal for subjects are between 26 to 35 umol/L, Para. [0094]). regarding claim 12, Scharschmidt discloses the method of claim 6. Scharschmidt discloses further comprising: c) measuring urinary PAGN excretion (measuring PAGN excretion, Para. [0096]); and e) determining an effective dosage of the PAA (effective dose, Para. [0140]), prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60-75% (determining an amount of the PAA prodrug needed to mobilize the target amount of urinary PAGN based on about 60% to about 75% conversion of the PAA prodrug into urinary PAGN, Para. [0148]).

Regarding claim 12, Scharschmidt discloses the method of claim 6. Scharschmidt discloses further comprising: c) measuring urinary PAGN excretion (measuring PAGN excretion, Para. [0096]); and

e) determining an effective dosage of the PAA (effective dose, Para. [0140]), prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60-75% (determining an amount of the PAA prodrug needed to mobilize the target amount of urinary PAGN based on about 60% to about 75% conversion of the PAA prodrug into urinary PAGN, Para. [0148]).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scharschmidt (US 2010/0008859) in view of Ennis et al. (The New England Journal of Medicine, 2007, 356; pages 2282-92, Both references are cited in the IDS dated 06/28/2012).

Scharschmidt discloses the method (method, Para. [0039]) for determining whether to increase a dosage of a nitrogen scavenging drug in a subject (adjusting the schedule and dose of orally administered nitrogen scavenging drugs, Para. [0020]) currently receiving the nitrogen scavenging drug (method involves administering an initial dosage of the prodrug that is selected based on the patient's current dosage (already receiving a drug), Para. [0044]) comprising: a) measuring a fasting blood ammonia level (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject (subjects, Para. [0213]); b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level ((comparing fasting with) normal upper limit for venous (blood) ammonia, Para. [0201], plasma upper limit of normal, Para. [0094]) to determine whether to increase the dosage of a nitrogen scavenging drug (determining and adjusting the dose of an ammonia scavenging drug, Para. [0041]), wherein the dosage needs to be increased if the fasting blood ammonia level is greater than half

the upper limit of normal for blood ammonia level (If the ammonia control is inadequate, the dosage of the nitrogen scavenging drug can be increased, Para. [0083]; ammonia value after HPN-100 treatment (26.1 umol/L) was within the normal range and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximately 26 to 35 umol/L; half the upper limit of normal is about 13 to 17.5 umol/L which is greater than 26.1 umol/L), Para. [0201]).

Regarding claim 2, Scharschmidt discloses the method (method, Para. [0039]) for determining whether to administer a nitrogen scavenging drug by adjusting the schedule and dose of orally administered nitrogen scavenging drugs, Para. [0020]) to a subject having a nitrogen retention disorder (retention states including urea cycle disorders and liver disease, Para. [0064]) comprising: a) measuring a fasting blood ammonia level for the subject (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject (subjects, Para. [0213]); and b) comparing the fasting blood ammonia level to the upper limit of normal for blood ((comparing) normal upper limit for venous (blood) ammonia, Para. [0201], plasma upper limit of normal, Para. [0094]) ammonia levels to determine whether to administer a nitrogen scavenging drug to the subject (determining the dose of an ammonia scavenging drug to be administered, Para. [0041]), wherein a nitrogen scavenging drug needs to be administered to the subject if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level (adjusting the initial dosage of the new drug based upon ammonia control, Para. [0099]; (ammonia value after HPN-100 treatment (26.1 umol/L) was within the normal range and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximately 26 to 35 umol/L; half the upper limit of normal is about 13 to 17.5 umol/L which is greater than 26.1 umol/L), Para. [0201]).

Regarding claim 3, Scharschmidt discloses the method (method, Para. [0039]) of treating a subject with a nitrogen retention disorder (dosing schedule and dose adjustments necessary for treatment of nitrogen retention states including urea cycle disorders and liver disease complicated by hepatic encephalopathy, Para. [0064]) who has previously been administered a nitrogen scavenging drug (method involves administering an initial dosage of the prodrug that is selected based on the patient's current dosage (already receiving a drug), Para. [0044]) comprising: a) measuring a fasting blood ammonia level (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212])

for the subject (subjects, Para. [0213]); and b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level and administering an increased dosage of the nitrogen scavenging drug (If the ammonia control is inadequate, the dosage of the nitrogen scavenging drug can be increased, Para. [0083]) if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level (ammonia value after HPN-100 (26.1 umol/L) was within the normal range of 26 to 35 umol/L and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximately 26 to 35 umol/L; half the upper limit of normal is about 13 to 17.5 umol/L which is greater than 26.1 umol/L), Para. [0201]).

Regarding claim 4, Scharschmidt discloses the method of claim 1. Scharschmidt discloses further comprising: c) administering an increased dosage of the nitrogen scavenging drug if the need exists (treatment with an ammonia scavenging agent as described in this invention is determined clinically if the subject is in need of such treatment. This clinical determination would be based upon a variety of factors (e.g. signs and symptoms of hepatic encephalopathy in patients with cirrhosis, elevated blood ammonia levels), Para. [0221]);

Regarding claim 5, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses wherein the nitrogen retention disorder is selected from the group consisting of a urea cycle disorders and hepatic encephalopathy (urea cycle disorder, Para. [0221], hepatic encephalopathy, Para. [0041]).

Regarding claim 6, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses wherein the nitrogen scavenging drug is a PAA prodrug (prodrugs of PAA, Para. [0217]).

Regarding claim 7, Scharschmidt discloses the method of claim 6. Scharschmidt discloses wherein the PAA prodrug is selected from the group consisting of glyceryl td-[4-phenylbutyrate] (HPN-100), phenylbutyric acid (PBA), sodium PBA (NaPEA), and a combination of two or more of HPN-100, PBA, and NaPBA (HPN-100, Para. [0020]).

Regarding claim 9, Scharschmidt discloses the method of claim 3 or 4. Scharschmidt discloses wherein administering an increased dosage of the nitrogen scavenging drug produces a normal average daily ammonia level in the subject (administering the effective dosage of HPN-100 (effective dose may

require increasing or decreasing the drug) to the patient preferably produces a normal plasma ammonia level in the patient, Para. [0142]); nitrogen scavenging drug may need to be increased, Para. [0083]).

Regarding claim 10, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses further comprising the step of determining an upper limit of normal for blood ammonia level for the subject prior to step (b) (monitoring the effect of the initial dosage of HPN-100 consists essentially of determining the patient's urinary phenylacetyl glutamine (PAGN) output and/or total urinary nitrogen. Administering the effective dose of HPN-100 to the patient produces a normal plasma ammonia level. Plasma ammonia in the patient can be a level of about 35 or about 40 umol/L (determining the upper limit of normal for the subject via urinary excretion of PAGN prior to step b), Para. [0142]); the normal upper limit for venous (blood) ammonia varied among the study sites from 26 to 35 umol/L, Para. [0201]).

Regarding claim 11, Scharschmidt discloses the method of any of claims 1-3. Scharschmidt discloses wherein the upper limit of normal blood ammonia level is 35 umol/L (upper limit of normal for subjects are between 26 to 35 umol/L, Para. [0094]). regarding claim 12, Scharschmidt discloses the method of claim 6. Scharschmidt discloses further comprising: c) measuring urinary PAGN excretion (measuring PAGN excretion, Para. [0096]); and e) determining an effective dosage of the PAA (effective dose, Para. [0140]), prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60-75% (determining an amount of the PAA prodrug needed to mobilize the target amount of urinary PAGN based on about 60% to about 75% conversion of the PAA prodrug into urinary PAGN, Para. [0148]).

Regarding claim 12, Scharschmidt discloses the method of claim 6. Scharschmidt discloses further comprising: c) measuring urinary PAGN excretion (measuring PAGN excretion, Para. [0096]); and e) determining an effective dosage of the PAA (effective dose, Para. [0140]), prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60-75% (determining an amount of the PAA prodrug needed to mobilize the target amount of urinary PAGN based on about 60% to about 75% conversion of the PAA prodrug into urinary PAGN, Para. [0148]).

Scharschmidt fails to explicitly disclose wherein the nitrogen scavenging drug is sodium benzoate.

However, Ennis is in the field of treating urea cycle disorders with phenylacetate and benzoate and teaches the use of sodium benzoate to treat patients with ammonia disorders (sodium benzoate therapy in patients, Pg. 1, Lns.1-16). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the therapeutic drug sodium benzoate as taught by Ennis with the method of Scharschmidt. The motivation would have been to lower plasma ammonium levels and improve the survival of patients with lethal urea-cycle enzyme defects (Ennis, lower plasma ammonium levels and improve survival in small cohorts of patients with historically lethal urea-cycle enzyme defects, Pg. 1, Lines. 1-16).

Conclusion

Claims 1-12 are rejected.

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 7.00 AM to 4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/SAVITHA RAO/

Primary Examiner, Art Unit 1629

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13417137	SCHARSCHMIDT ET AL.
	Examiner	Art Unit
	SAVITHA RAO	1629

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (see attached)	11/16/2012	SR
inventor search in EAST and PALM	11/16/2012	SR
STN search for NPL and patents (see attached)	11/16/2012	SR

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

	/SAVITHA RAO/ Primary Examiner.Art Unit 1629

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **SCHARSCHMIDT, Bruce, et al.** **Serial No.:** 13/417,137 **Filed:** March 9, 2012 **For: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS**	**Examiner:** RAO, Savitha M. **Group Art Unit:** 1629 **Docket No.:** 79532.8003.US02 I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is being deposited with the U.S. Patent and Trademark Office this 7th day of December 2012 via EFS-Web Electronic Filing. / Colleen Kirchner / Colleen Kirchner

AMENDMENT AND RESPONSE

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

Sir:

The following is in response to the Non-Final Office Action mailed November 21, 2012 for the above-identified application.

Amendments to the claims begin on page 2.

Remarks begin on page 4.

Conclusion begins on page 10.

REMARKS

Initial comments

Claims 1-12 are pending in the present application and stand rejected.

Applicant has amended independent claims 1-3. Claims 1 and 2 have been amended to recite a method of adjusting and a method of administering, respectively, rather than simply a method of determining whether to adjust or administer. Accordingly, both claims now include an active step of administering a nitrogen scavenging drug or an adjusted dosage of a nitrogen scavenging drug. Claim 3 has been amended to clarify the meaning of the dosages recited therein. Amended claims 1-3 all retain the fundamental steps of measuring a fasting blood ammonia level and comparing this level to the upper limit of normal, wherein a fasting blood ammonia level greater than half the upper limit of normal triggers administration of a nitrogen scavenging drug or administration of an increased dosage of a nitrogen scavenging drug.

Claim 4 has been canceled as redundant in light of the amendments to claim 1, while claim 12 has been amended to correct a typographical error.

Anticipation

Rejection

The Office Action rejects claims 1-7 and 9-12 as anticipated by US Patent Publication No. 2010/0008859 ("Scharschmidt"). With regard to independent claim 1, the Office Action states:

> Scharschmidt discloses the method…for determining whether to increase the dosage of a nitrogen scavenging drug in a subject (adjusting the schedule of and dose of orally administered nitrogen scavenging drugs, Para. [0020]) currently receiving the nitrogen scavenging drug (method involves administering an initial dosage of the prodrug that is selected based on the patient's current dosage (already receiving a drug), Para. [0044]) comprising: a) measuring a fasting blood ammonia level (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject…b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level ((comparing fasting with) normal upper limit for venous (blood) ammonia, Para. [0201], plasma upper limit of normal, Para. [0094]) to determine whether to increase the dosage of a nitrogen scavenging drug…wherein the dosage needs to be increased if the fasting blood ammonia level is greater than

> half the upper limit of normal for blood ammonia level (if the ammonia control is inadequate, the dosage of the nitrogen scavenging drug can be increased, Para. [0083]; ammonia value after HPN-100 treatment (26.1 μmol/L) was within the normal range and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximately 26 to 35 μmol/L; half the upper limit of normal is about 13 to 17.5 μmol/L which is greater than 26.1 μmol/L, Para. [0201]).

With regard to independent claim 2, the Office Action states:

> Scharschmidt discloses the method…for determining whether to administer a nitrogen scavenging drug (adjusting the schedule and dose of orally administered nitrogen scavenging drugs, Para. [0020]) to a subject having a nitrogen retention disorder (retention states including urea cycle disorders and liver disease, Para. [0064]) comprising: a) measuring a fasting blood ammonia level for the subject (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject…and b) comparing the fasting blood ammonia level to the upper limit of normal for blood ((comparing) normal upper limit to venous (blood) ammonia, Para. [0201], plasma upper limit of normal, Para. [0094]) to determine whether to administer a nitrogen scavenging drug…wherein a nitrogen scavenging drug needs to be administered if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level (adjusting the initial dosage of the new drug based upon ammonia control, Para. [0099]; (ammonia value after HPN-100 treatment (26.1 μmol/L) was within the normal range and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximately 26 to 35 μmol/L; half the upper limit of normal is about 13 to 17.5 μmol/L which is greater than 26.1 μmol/L), Para. [0201]).

With regard to independent claim 3, the Office Action states:

> Scharschmidt discloses the method…of treating a subject with a nitrogen retention disorder (dosing schedule and dose adjustments…) who has previously been administered a nitrogen scavenging drug (method involves administering an initial dosage of the prodrug that is selected based on the patient's current dosage (already receiving a drug), Para. [0044]) comprising: a) measuring a fasting blood ammonia level (PK/PD modeling (a measurement) of ammonia in fasted and fed (subjects), Para. [0212]) for the subject (subjects, Para. [0213]); and b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level and administering an increased dosage of the nitrogen scavenging drug (if the ammonia control is inadequate, the dosage of the nitrogen scavenging drug can be increased, Para. [0083]) if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level (ammonia value after HPN-100 (26.1 μmol/L) was

> within the normal range of 26 to 35 μmol/L and above the upper limit of normal (ULN) after sodium PB (upper limit of normal is approximately 26 to 35 μmol/L; half the upper limit of normal is about 13 to 17.5 μmol/L which is greater than 26.1 μmol/L), Para. [0201]).

The Office Action goes on to address each of dependent claims 4-7 and 9-12 in detail by citing portions of Scharschmidt that allegedly disclose the various limitations of each claim.

Response

As acknowledged in the background section of the present application, it is well known in the art that nitrogen retention disorders are associated with elevated blood ammonia levels, and that these disorders can be treated by administering nitrogen scavenging drugs. The Office Action is correct that Scharschmidt discloses methods of determining whether to increase the dosage of a nitrogen scavenging drug, methods of determining whether to administer a nitrogen scavenging drug, and methods of treating nitrogen retention disorders by administering a nitrogen scavenging drug in a particular manner. These methods are based on the finding in Scharschmidt that blood PBA, PAA, and PAGN levels are unreliable indicators of PAA prodrug dosage efficacy, and that urinary PAGN is a more reliable biomarker for PAA prodrug dosage evaluation. Scharschmidt provides experimental results showing that the percent conversion of HPN-100 to urinary PAGN varies significantly from patient to patient, with an average percent conversion of approximately 60-75% (Examples 2 and 3), and that administration of HPN-100 results in more effective control of ammonia levels than sodium PBA. Scharschmidt's claimed methods are based on these findings regarding the relationship between urinary PAGN levels and drug efficacy.

Scharschmidt only briefly mentions the upper limit of normal for ammonia. Specifically, Scharschmidt states at paragraph 0094 that "In certain clinical tests described herein the upper limit of normal for the subjects was between 26 and 35 μmol/L." This represents a fairly standard range for the upper limit of normal in a nitrogen retention disorder population, which varies somewhat from laboratory to laboratory. At paragraph 0201 (Example 3), Scharschmidt states that the "normal upper limit for venous ammonia varied among the study sites from 26 to 35 μmol/L," and that "patients with higher ammonia

levels on sodium PBA exhibited greater decreases in ammonia values following administration of HPN-100." Paragraph 0201 goes on to state that "the mean ammonia value after HPN-100…was within the normal range while it was above the upper limit of normal (ULN) after sodium PBA." This paragraph simply reiterates the upper limit of normal observed in the clinical population being examined in Scharschmidt, and notes that HPN-100 lowered mean ammonia level to below the upper limit of normal while sodium PBA did not (i.e., HPN-100 was more effective than sodium PBA). This is reiterated in paragraph 0209, in which Scharschmidt states that "ammonia levels were better controlled in this test by HPN-100 than with sodium PBA, e.g., the average ammonia levels are lower, and tend to be below the upper limit for normal."

The present claims are based on a detailed investigation of the relationship between fasting blood ammonia levels and daily ammonia exposure. As noted in the present application, a single random ammonia value is an unreliable indicator of a subject's actual daily ammonia exposure, and hence an unreliable indicator of nitrogen scavenging drug dosing efficacy. The present application provides experimental results showing that a fasting ammonia level greater than half the upper limit of normal indicates unsatisfactory nitrogen control. This is a novel and unexpected finding, because it suggests that a subject with a fasting nitrogen level below the upper limit of normal may nonetheless require an increased dosage of nitrogen scavenging drug to achieve satisfactory daily ammonia levels. Accordingly, each of the independent claims includes steps of measuring fasting blood ammonia level and comparing it to the upper limit of normal for blood ammonia level to determine whether it is greater than half the upper limit of normal. If the fasting blood ammonia level is greater than half the upper limit of normal, the claims call for increasing the dosage of a nitrogen scavenging drug (claims 1 and 3) or administering a nitrogen scavenging drug (claim 2).

Although Scharschmidt mentions the upper limit of normal for ammonia, it does not teach or suggest the use of fasting ammonia levels in evaluating nitrogen scavenging drug dosage, and it certainly does not teach or suggest that a fasting ammonia level greater than half the upper limit of normal indicates a need for increased drug dosage. In noting that

HPN-100 was more effective than sodium PBA at controlling ammonia levels, Scharschmidt states that HPN-100 resulted in ammonia levels below the upper limit of normal. Based on the findings in the present application, such a result would be insufficient on its own to establish optimal dosage levels. Specifically, Scharschmidt discloses that HPN-100 treatment resulted in a blood ammonia level of 26.1 μmol/L versus an upper limit of normal of about 26 to 35 μmol/L. As noted in the Office Action, half of the upper limit of normal disclosed in Scharschmidt is about 13 to 17.5 μmol/L. Since the measured blood ammonia level was greater than half the upper limit of normal (Applicant notes that the Office Action is incorrect in repeatedly stating that "half the upper limit of normal is about 13 to 17.5 μmol/L *which is greater than* 26.1 μmol/L"), the results proffered by Scharschmidt to indicate efficacy of HPN-100 actually suggest a need for an increased dosage of the drug to achieve optimal ammonia control.

Given the lack of disclosure in Scharschmidt regarding the relationship between the upper limit of normal and nitrogen scavenging drug dosage efficacy, Scharschmidt fails to teach each and every element of the present claims.

Obviousness

Rejection

The Office Action rejects claims 1-12 as obvious Scharschmidt in view of Enns N Engl J Med 356:2282 (2007) ("Enns"). The Office Action acknowledges that Scharschmidt "fails to explicitly disclose wherein the nitrogen scavenging drug is sodium benzoate," but asserts that Enns "is in the field of treating urea cycle disorders with phenylacetate and benzoate and teaches the use of sodium benzoate to treat patients with ammonia disorders." As such, the Office Action asserts that it would have been obvious to use sodium benzoate as taught by Enns with the method of Scharschmidt, with the motivation being the lowering of plasma ammonium levels and improved survival for patients with urea cycle enzyme defects.

Response

As discussed in the background of the present application, sodium benzoate is a well-known nitrogen scavenging agent, and Applicant acknowledges that Enns teaches the use of sodium benzoate to treat various nitrogen retention disorders. However, Enns does not contain disclosure sufficient to overcome the various deficiencies of Scharschmidt discussed

above. Specifically, Enns does not teach or suggest the relationship between fasting ammonia levels and the upper limit of normal for blood ammonia, or the use of this relationship in optimizing nitrogen scavenging drug dosage.

CONCLUSION

In view of the foregoing, it is submitted that the present claims are in condition for allowance. Accordingly, Applicant respectfully requests that a Notice of Allowance be issued. If Applicant can do anything more to expedite this application, Applicant requests that the Examiner contact the undersigned at (650) 838-4355.

Respectfully submitted,
Perkins Coie LLP

Date: December 7, 2012

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AMENDMENTS TO THE CLAIMS

The following complete listing of claims replaces all previous claims in the application. Applicant has amended claims 1-3 and 12, and canceled claim 4.

1. (currently amended) A method for adjusting the ~~determining whether to increase a~~ dosage of a nitrogen scavenging drug in a subject who has previously been administered an initial dosage of ~~currently receiving~~ the nitrogen scavenging drug, comprising:

a) measuring a fasting blood ammonia level for the subject; ~~and~~

b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level ~~to determine whether to increase the dosage of a nitrogen scavenging drug,~~; and

c) administering an adjusted dosage of the nitrogen scavenging drug, wherein the adjusted dosage is greater than the initial ~~wherein the~~ dosage ~~needs to be increased~~ if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.

2. (currently amended) A method of administering ~~for determining whether to administer~~ a nitrogen scavenging drug to a subject having a nitrogen retention disorder comprising:

a) measuring a fasting blood ammonia level for the subject; ~~and~~

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

c) ~~to determine whether to~~ administering the [[a]] nitrogen scavenging drug to the subject~~, wherein a nitrogen scavenging drug needs to be administered to the subject~~ if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.

3. (currently amended) 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; ~~and~~

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

c) administering an adjusted ~~increased~~ 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.

4. (canceled)

5. (original) The method of any of claims 1-3, wherein the nitrogen retention disorder is selected from the group consisting of a urea cycle disorder and hepatic encephalopathy.

6. (original) The method of any of claims 1-3, wherein the nitrogen scavenging drug is a PAA prodrug.

7. (original) The method of claim 6, wherein the PAA prodrug is selected from the group consisting of glyceryl tri-[4-phenylbutyrate] (HPN-100), phenylbutyric acid (PBA), sodium PBA (NaPBA), and a combination of two or more of HPN-100, PBA, and NaPBA.

8. (original) The method of any of claims 1-3, wherein the nitrogen scavenging drug is sodium benzoate.

9. (original) The method of claim 3 or 4, wherein administering an increased dosage of the nitrogen scavenging drug produces a normal average daily ammonia level in the subject.

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

11. (original) The method of any of claims 1-3, wherein the upper limit of normal blood ammonia level is 35 μmol/L.

12. (currently amended) The method of claim 6, further comprising:

d [[c]]) measuring urinary PAGN excretion; and

e) determining an effective dosage of the PAA prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60-75%.

Electronic Acknowledgement Receipt	
EFS ID:	14414441
Application Number:	13417137
International Application Number:	
Confirmation Number:	6423
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Patrick D. Morris/Colleen Kirchner
Filer Authorized By:	Patrick D. Morris
Attorney Docket Number:	79532.8003.US02
Receipt Date:	07-DEC-2012
Filing Date:	09-MAR-2012
Time Stamp:	15:59:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		OAResponse.pdf	119786 cc67f3b37e264024b014ae9c8da695b84cb93e9a	yes	10

	Multipart Description/PDF files in .zip description		
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	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	10
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APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/07/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 27	= 0	X $31 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $125 =	0	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	0	OR	TOTAL ADD'L FEE	

AMENDMENT		(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".
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Legal Instrument Examiner:
/DORIS BURNS/

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 NEWS 29  AUG  1  Reload of ReaxysFile on STN - Significantly More Content Added
                  and Updates are Resumed
 NEWS 30  AUG  1  Redesigned CAS Website to be Launched on August 5, 2012
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 NEWS 31  AUG  6  INPADOC: German Patent Coverage Resumed
 NEWS 32  SEP 10  Get More Current Reaction Information with Daily Updates to
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REVISED CLASS FIELDS (/NCL) LAST RELOADED:  September 2012
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  September 2012

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

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

=> d l2 ibib ab

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

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              0 BUTYRIC
L3            0 L1 AND BUTYRIC

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=> s nitrogen
L5            0 NITROGEN
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REVISED CLASS FIELDS (/NCL) LAST RELOADED:  September 2012
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  September 2012

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

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substance identification.

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

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

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

=> d l8 ibib ab

L8   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:        2010:708850  CAPLUS
DOCUMENT NUMBER:         154:477123
TITLE:                   Phase 2 comparison of a novel ammonia scavenging
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agent with sodium phenylbutyrate in patients with urea cycle disorders: Safety, pharmacokinetics and ammonia control

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

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

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

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

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

OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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

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

=> d l11 1-9 ibib ab

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

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

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 101954091	A	20110126	CN 2010-10507432	20101014
PRIORITY APPLN. INFO.:			CN 2010-10507432	20101014

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

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

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

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

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

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

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

L11 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2000:890604 CAPLUS

DOCUMENT NUMBER: 134:242530

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

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

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

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

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

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

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

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

L11 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 1997:5450 CAPLUS

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

CORPORATE SOURCE: Univ. California, USA

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

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

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

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

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


=> d his

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

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

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

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

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                 Organization Becomes 63rd Authority on CA/CAplus
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                 Numerical Property Search Feature
NEWS  5  APR 23  RSS Delivery for STN Alerts (SDIs) is Now Available on STN
NEWS  6  MAY  9  INIS, BABS and GMELIN97 Databases Removed from STN
NEWS  7  MAY 21  Reload of FSTA Database
NEWS  8  MAY 21  Search DOIs in CA/CAplus on STN
NEWS  9  MAY 23  Get the Latest Version of STN Express, Version 8.5.1!
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NEWS 11  MAY 30  INPADOC Databases-Enhanced Coverage of US Citation Data
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NEWS 13  JUN 11  Keep Current with Weekly SDI Packages Now Available on STN
NEWS 14  JUL 05  More Frequent Updates to the Emtree Thesaurus in Embase on STN
                 Provide Earlier Access to the Latest Drug and Medical
                 Terminology
NEWS 15  JUL 18  INPADOCDB: Enhanced Display Options
NEWS 16  JUL 19  Upcoming Reload of AEROSPACE: Effect on SDIs, Manual
                 Profiles and Saved Answers
NEWS 17  JUL 30  Launch of new PQSciTech Database, Created from 25 Individual
                 CSA Databases Allows More Efficient Searching on STN
NEWS 18  JUL 30  Reload of ENCOMPPAT/2 Databases
NEWS 19  JUL 30  More Experimental Property Data in CAS REGISTRY
NEWS 20  AUG  1  Reload of ReaxysFile on STN - Significantly More Content Added
                 and Updates are Resumed
NEWS 21  AUG  1  Redesigned CAS Website to be Launched on August 5, 2012
NEWS 22  AUG  6  INPADOC: German Patent Coverage Resumed
NEWS 23  SEP 10  Get More Current Reaction Information with Daily Updates to
                 CASREACT
NEWS 24  SEP 10  Predict when CAS REGISTRY Hits 70 Million
NEWS 25  SEP 20  Reload of METADEX - Effect on SDIs and Saved Answers
NEWS 26  SEP 24  Expanded Embase Database Coverage on STN Includes More
                 Biomedical and Pharmacological Content from Conferences
NEWS 27  OCT 19  MARPAT Backfile Expansion Update
NEWS 28  OCT 23  Embase's Emtree Thesaurus Updated
NEWS 29  OCT 29  New Japanese Full-Text Patent Database Now Available on STN
NEWS 30  NOV 13  Upcoming Reload of AGRICOLA - Effect on SDIs, Manual Profiles
                 and Saved Answers
NEWS 31  NOV 19  Reload of IMSPATENTS - Effect on SDIs, Manual profiles and
                 Saved answers
NEWS 32  NOV 27  INPADOC: The New Cooperative Patent Classification Is Now
                 Available.
NEWS 33  DEC  3  Enhanced CASREACT Coverage on STN - A New Source of Prior Art
NEWS 34  DEC 10  New SDI STANDARD Option Streamlines SDI Set-ups on STN

NEWS EXPRESS 23 MAY 2012 CURRENT WINDOWS VERSION IS V8.5.1,
             AND CURRENT DISCOVER FILE IS DATED 11 DECEMBER 2012.

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=> file caplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
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FULL ESTIMATED COST                                         0.24       0.24

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USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  November 2012

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

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

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

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

=> d l2 1-11 ibib ab

L2   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:        2012:1307676  CAPLUS
TITLE:                   Urinary phenylacetylglutamine as dosing biomarker for
                         patients with urea cycle disorders
AUTHOR(S):               Mokhtarani, M.; Diaz, G. A.; Rhead, W.;
                         Lichter-Konecki, U.; Bartley, J.; Feigenbaum, A.;
                         Longo, N.; Berquist, W.; Berry, S. A.; Gallagher, R.;
                         Bartholomew, D.; Harding, C. O.; Korson, M. S.;
                         McCandless, S. E.; Smith, W.; Vockley, J.; Bart, S.;
                         Kronn, D.; Zori, R.; Cederbaum, S.; Dorrani, N.;
                         Merritt, J. L.; Sreenath-Nagamani, Sandesh; Summar,
                         M.; LeMons, C.; Dickinson, K.; Coakley, D. F.; Moors,
                         T. L.; Lee, B.; Scharschmidt, B. F.
CORPORATE SOURCE:        601 Gateway Blvd, Hyperion Therapeutics, South San
                         Francisco, CA, 94080, USA
SOURCE:                  Molecular Genetics and Metabolism (2012), 107(3),
                         308-314
                         CODEN: MGMEFF; ISSN: 1096-7192
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal; (online computer file)
LANGUAGE:                English
AB   We have analyzed pharmacokinetic data for glycerol phenylbutyrate (also
     GT4P or HPN-100) and sodium phenylbutyrate with respect to possible dosing
     biomarkers in patients with urea cycle disorders (UCD).These analyses are
     based on over 3000 urine and plasma data points from 54 adult and 11
     pediatric UCD patients (ages 6-17) who participated in three clin. studies
     comparing ammonia control and pharmacokinetics during steady state
     treatment with glycerol phenylbutyrate or sodium phenylbutyrate.  All
     patients received phenylbutyric acid equivalent doses of glycerol
     phenylbutyrate or sodium phenylbutyrate in a cross over fashion and
     underwent 24-h blood samples and urine sampling for phenylbutyric acid,
     phenylacetic acid and phenylacetylglutamine.Patients received
     phenylbutyric acid equivalent doses of glycerol phenylbutyrate ranging from
     1.5 to 31.8 g/day and of sodium phenylbutyrate ranging from 1.3 to 31.7
     g/day.  Plasma metabolite levels varied widely, with average fluctuation
     indexes ranging from 1979% to 5690% for phenylbutyric acid, 843% to 3931%
     for phenylacetic acid, and 881% to 1434% for phenylacetylglutamine.  Mean
     percent recovery of phenylbutyric acid as urinary phenylacetylglutamine
     was 66.4 and 69.0 for pediatric patients and 68.7 and 71.4 for adult
     patients on glycerol phenylbutyrate and sodium phenylbutyrate, resp.  The
     correlation with dose was strongest for urinary phenylacetylglutamine
     excretion, either as morning spot urine (r = 0.730, p < 0.001) or as total
     24-h excretion (r = 0.791 p < 0.001), followed by plasma
     phenylacetylglutamine AUC24-hour, plasma phenylacetic acid AUC24-hour and
     phenylbutyric acid AUC24-hour.  Plasma phenylacetic acid levels in adult
     and pediatric patients did not show a consistent relationship with either
     urinary phenylacetylglutamine or ammonia control.The findings are
     collectively consistent with substantial yet variable pre-systemic (1st
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pass) conversion of phenylbutyric acid to phenylacetic acid and/or phenylacetylglutamine. The variability of blood metabolite levels during the day, their weaker correlation with dose, the need for multiple blood samples to capture trough and peak, and the inconsistency between phenylacetic acid and urinary phenylacetylglutamine as a marker of waste nitrogen scavenging limit the utility of plasma levels for therapeutic monitoring. By contrast, 24-h urinary phenylacetylglutamine and morning spot urine phenylacetylglutamine correlate strongly with dose and appear to be clin. useful non-invasive biomarkers for compliance and therapeutic monitoring.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:1307575 CAPLUS
TITLE: Recurrent unexplained hyperammonemia in an adolescent with arginase deficiency
AUTHOR(S): Zhang, Yan; Landau, Yuval E.; Miller, David T.; Marsden, Deborah; Berry, Gerard T.; Kellogg, Mark D.
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, USA
SOURCE: Clinical Biochemistry (2012), 45(18), 1583-1586
CODEN: CLBIAS; ISSN: 0009-9120
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB This report investigates the etiol. of recurrent episodic elevations in plasma ammonia in an adolescent male with arginase deficiency as there were concerns regarding pre-anal. and anal. perturbations of ammonia measurements. There were repeated discrepancies between the magnitude of his ammonia levels and the severity of his clin. signs of hyperammonemia.The patient is a fourteen-year-old arginase-deficient male diagnosed at three years of age. Since 2008 (when he reached 10 years of age), there appeared to be an increase in the frequency of hospitalizations with elevated ammonia. A typical emergency visit with initial ammonia of 105 μmol/L (reference interval: 16-47 μmol/L) is illustrated. Pre-anal. and anal. procedures for the patient's sample handling were retrospectively examd.His ammonia levels were compiled since diagnosis. The frequency of his initial or peak ammonia levels greater than two times (94 μmol/L) or four times (188 μmol/L) the upper limit of normal was computed. Student t-test was used to calculate the significance of the differences before 2008 and since 2008.One out of eleven and ten out of 19 hospitalizations had initial ammonia greater than two times normal before and after 2008, resp. Both the patient's overall ammonia and peak ammonia levels are significantly higher since 2008 (p value < 0.001 for both) than those before 2008.To our knowledge, few adolescent males with arginase deficiency experience recurrent episodes of hyperammonemia requiring i.v. nitrogen scavenging agents. We hope that this study provides new insights into the natural history of arginase deficiency and the management of such patients.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:661267 CAPLUS
TITLE: Argininosuccinate lyase deficiency
AUTHOR(S): Nagamani, Sandesh C. S.; Erez, Ayelet; Lee, Brendan
CORPORATE SOURCE: Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA
SOURCE: Genetics in Medicine (2012), 14(5), 501-507
CODEN: GEMEF3; ISSN: 1098-3600

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

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

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

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

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

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

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

L2 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN

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

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

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

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:397345 CAPLUS
DOCUMENT NUMBER: 155:453598
TITLE: Lysinuric protein intolerance: reviewing concepts on a multisystem disease
AUTHOR(S): Sebastio, Gianfranco; Sperandeo, Maria P.; Andria, Generoso
CORPORATE SOURCE: Department of Clinical Pediatrics, Federico II University of Naples, Italy
SOURCE: American Journal of Medical Genetics, Part C: Seminars in Medical Genetics (2011), 157(1), 54-62
CODEN: AJMGFC; ISSN: 1552-4868
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Lysinuric protein intolerance (LPI) is an inherited aminoaciduria caused by defective cationic amino acid transport at the basolateral membrane of epithelial cells in intestine and kidney. LPI is caused by mutations in the SLC7A7 gene, which encodes the y+LAT-1 protein, the catalytic light chain subunit of a complex belonging to the heterodimeric amino acid transporter family. LPI was initially described in Finland, but has worldwide distribution. Typically, symptoms begin after weaning with refusal of feeding, vomiting, and consequent failure to thrive. Hepatosplenomegaly, hematol. anomalies, neurol. involvement, including hyperammonemic coma are recurrent clin. features. Two major complications, pulmonary alveolar proteinosis and renal disease are increasingly observed in LPI patients. There is extreme variability in the clin. presentation even within individual families, frequently leading to misdiagnosis or delayed diagnosis. This condition is diagnosed by urine amino acids, showing markedly elevated excretion of lysine and other dibasic amino acids despite low plasma levels of lysine, ornithine, and arginine. The biochem. diagnosis can be uncertain, requiring confirmation by DNA testing. So far, approx. 50 different mutations have been identified in the SLC7A7 gene in a group of 142 patients from 110 independent families. No genotype-phenotype correlation could be established. Therapy requires a low protein diet, low-dose citrulline supplementation, nitrogen-scavenging compds. to prevent hyper-ammonemia, lysine, and carnitine supplements. Supportive therapy is available for most complications with bronchoalveolar lavage being necessary for alveolar proteinosis.

OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD

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

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

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

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

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010025303	A1	20100304	WO 2009-US55256	20090827
WO 2010025303	A9	20100624		
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
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WO 2009134460	A1	20091105	WO 2009-US30362	20090107
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GB 2465250	A	20100519	GB 2009-15545	20090827
GB 2465250	B	20110126		
EP 2338050	A1	20110629	EP 2009-748559	20090827
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US 20120022157	A1	20120126	US 2011-61509	20110615

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

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

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

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

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

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

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

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

=> d his

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

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

L2 11 S L1 AND AMMONIA

=>

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	0	"13417137".rlan. or ("13".src. and "417137".ap.)	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 13:46
S2	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:46
S3	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:46
S4	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:56
S5	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 13:56
S6	0	((MASOUD) near2 (MOKHTARANI)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:56
S7	18	("20040229948" | "20060135612" | "4284647" | "6083984" | "20080119554" | "6219567" | "20100008859" | "6050510" | "5968979" | "20100008859" | "6219567").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/11/15 13:57
S8	0	S1 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S9	8	S7 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S10	2	S9 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S11	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:12
S12	4	S11 and PAA	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:12
S13	4	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/15 14:13
S14	9	((BRUCE) near2 (SCHARSCHMIDT)).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO;	OR	OFF	2012/11/15 14:13

			DERWENT; IBM_TDB			
S15	18	("4284647" | "6083984" | "6050510" | "6219567" | "20040229948" | "20080119554" | "20060135612" | "5968979" | "20100008859").PN.	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/16 07:11
S16	2	S15 and "nitrogen scavenging"	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/16 07:11
S17	1	("6083984").PN.	USPAT; USOCR	OR	OFF	2012/11/16 07:12
S18	9	((Saul) near2 (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" | "6219567").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 10:56
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; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:43
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;	OR	OFF	2012/12/20 16:43

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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;	OR	OFF	2012/12/20 16:43

			DERWENT			
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	4418	(424/9.2 514/533 514/433 514/432 73/61.41).ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/12/20 16:59

12/20/2012 8:32:54 PM
C:\Users\srao3\Documents\EAST\Workspaces\13417137.wsp

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13417137	SCHARSCHMIDT ET AL.
	Examiner	Art Unit
	SAVITHA RAO	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

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

CLAIM		DATE								
Final	Original	12/20/2012								
1	1	=								
2	2	=								
3	3	=								
-	4	-								
4	5	=								
5	6	=								
6	7	=								
7	8	=								
8	9	=								
9	10	=								
10	11	=								
11	12	=								

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
13417137	SCHARSCHMIDT ET AL.
Examiner	**Art Unit**
SAVITHA RAO	1629

ORIGINAL	
CLASS	SUBCLASS
424	9.2

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	533	433	432		

INTERNATIONAL CLASSIFICATION					
CLAIMED					NON-CLAIMED
A	6	1	K	49 / 00 (2006.0)	
A	6	1	P	13 / 00 (2006.01.01)	

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

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1														
2	2														
3	3														
-	4														
4	5														
5	6														
6	7														
7	8														
8	9														
9	10														
10	11														
11	12														

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	11	
/SAVITHA RAO/ Primary Examiner.Art Unit 1629	12/20/2012	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1

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NOTICE OF ALLOWANCE AND FEE(S) DUE

34055 7590 01/02/2013

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POST OFFICE BOX 1208
SEATTLE, WA 98111-1208

EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 01/02/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/417,137	03/09/2012	Bruce SCHARSCHMIDT	79532.8003.US02	6423

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

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$885	$300	$0	$1185	04/02/2013

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 SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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)

34055 7590 01/02/2013
PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE, WA 98111-1208

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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.
13/417,137	03/09/2012	Bruce SCHARSCHMIDT	79532.8003.US02	6423

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

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$885	$300	$0	$1185	04/02/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1629	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 credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

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

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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.

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Alexandria, Virginia 22313-1450
www.uspto.gov

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34055 7590 01/02/2013

PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE, WA 98111-1208

EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 01/02/2013

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

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

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 Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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.	Applicant(s)	
	13/417,137	SCHARSCHMIDT ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1629	

-- 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 *12/07/2012*.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-3 and 5-12*. 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).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

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

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

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

Attachment(s)

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

/SAVITHA RAO/
Primary Examiner, Art Unit 1629

DETAILED ACTION

Claims 1-3 and 5-12 are pending in the instant application.

REASONS FOR ALLOWANCE

In view of the applicants amendments and arguments filed on 12/07/2012 and the following examiners statement of reasons for allowance, claims 1-3 and 5-12 are found to be allowable.

Following a diligent search it was determined that the prior art neither teaches nor provides adequate motivation to arrive at the instantly claimed method for adjusting dosage of a nitrogen scavenging drug in a subject who has previously been administered an initial dosage of the nitrogen scavenging drug, and a method of administering a nitrogen scavenging drug to a subject having a nitrogen retention disorder or a method of treating a subject with nitrogen retention disorder who has previously been administered an initial dosage of 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, wherein the adjusted dosage is greater than the initial if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.

Conclusion

Claims 1-3 and 5-12 (renumbered 1-11) are allowed.

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

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melanie McCormick can be reached at 571-272-8037. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/SAVITHA RAO/

Primary Examiner, Art Unit 1629

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13417137	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SAVITHA RAO	1629

SEARCHED			
Class	**Subclass**	**Date**	**Examiner**
424	9.2	12/20/2012	SR
514	533, 433, 432	12/20/2012	SR

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
EAST search (see attached)	11/16/2012	SR
inventor search in EAST and PALM	11/16/2012	SR
STN search for NPL and patents (see attached)	11/16/2012	SR
updated EAST search (see attached)	12/20/2012	SR
updated inventor search in EAST	12/20/2012	SR
updated STN search for NPL and patents (see attached)	12/20/2012	SR

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**
424	7.2	12/20/2012	SR
514	533, 433, 432	12/20/2012	SR

	/SAVITHA RAO/ Primary Examiner.Art Unit 1629

Electronic Acknowledgement Receipt	
EFS ID:	15032264
Application Number:	13417137
International Application Number:	
Confirmation Number:	6423
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Michael J. Wise/Amy Candeloro
Filer Authorized By:	Michael J. Wise
Attorney Docket Number:	79532.8003.US02
Receipt Date:	22-FEB-2013
Filing Date:	09-MAR-2012
Time Stamp:	19:26:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1185
RAM confirmation Number	7735
Deposit Account	502586
Authorized User	
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 1.20 (Post Issuance fees)	

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)	2013-02-22_IssueFee_79532802US2.pdf	122178 b143c577d206dc04c813d4eeb4beb10500d16815	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31933 ccbaf6817a2240ce35d16163b80cc38e069faf45	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	154111		

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 Patent Application Fee Transmittal

Application Number:	13417137
Filing Date:	09-Mar-2012
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Filer:	Michael J. Wise/Amy Candeloro
Attorney Docket Number:	79532.8003.US02

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	2501	1	885	885
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1185**

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)

34055 7590 01/02/2013
PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE, WA 98111-1208

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.
13/417,137	03/09/2012	Bruce SCHARSCHMIDT	79532.8003.US02	6423

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

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$885	$300	$0	$1185	04/02/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1629	424-009200

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(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 Perkins Coie LLP
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: HYPERION THERAPEUTICS, INC.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): South San Francisco, CA

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 credit any overpayment, to Deposit Account Number 502586 (enclose an extra copy of this form).

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☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date February 22, 2013
Typed or printed name Patrick D. Morris Registration No. 53351

This collection of information 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.

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/417,137	03/26/2013	8404215	79532.8003.US02	6423

34055 7590 03/06/2013

PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE, WA 98111-1208

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)

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

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

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
13/417,137	03/09/2012	Bruce SCHARSCHMIDT	79532.8003.US02

CONFIRMATION NO. 6423

34055
PERKINS COIE LLP - LOS General
POST OFFICE BOX 1247
SEATTLE, WA 98111-1247

PUBLICATION NOTICE

OC000000060249150

Title:METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

Publication No.US-2013-0085179-A1
Publication Date:04/04/2013

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

Electronic Acknowledgement Receipt

EFS ID:	15480943
Application Number:	13417137
International Application Number:	
Confirmation Number:	6423
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Lauren Sliger/Colleen Kirchner
Filer Authorized By:	Lauren Sliger
Attorney Docket Number:	79532.8003.US02
Receipt Date:	10-APR-2013
Filing Date:	09-MAR-2012
Time Stamp:	14:08:52
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	Request for Certificate of Correction	CertificateofCorrection.pdf	52493 c21efe6754b43f7d4aa0e4894099e8dec7d4f57b	no	1

Warnings:	
Information:	

2	Request for Certificate of Correction	RequestCertificateCorrection.pdf	50146 96c1b491d8e963adaa8c85619e124daec9063d6a	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	102639	

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

National Stage of an International Application under 35 U.S.C. 371
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/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
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
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,404,215 B1
APPLICATION NO. : 13/417,137
ISSUE DATE : March 26, 2013
INVENTOR(S) : Bruce SCHARSCHMIDT et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Face page, in field (54) "TITLE", column 1, line 2, insert --DRUGS-- after "NITROGEN SCAVENGING".

Claim 2, column 24, line 45, insert --c)-- before "administering the nitrogen".

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Customer Number 34055
Perkins Coie LLP
P.O. Box 1208
Seattle, WA 98111-1208
Phone: (310) 788-9900

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: BRUCE SCHARSCHMIDT ET AL.
U.S. PATENT NO.: 8,404,215 B1
ISSUED: MARCH 26, 2013
FOR: METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. § 1.322

Attn: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. Applicants request a Certificate of Correction to correct the error in the above-identified patent listed on the enclosed Form PTO/SB/44.

2. The requested correction does not constitute new matter or require reexamination of the patent.

3. The error listed on Form PTO/SB/44 is believed to be due to mistake on the part of the USPTO (37 C.F.R. § 1.322). Accordingly, no fee is believed to be due.

4. Please send the Certificate of Correction to the undersigned at the address shown below.

Dated: April 10, 2013

Respectfully submitted,

PERKINS COIE LLP

By: /Patrick D. Morris/
Patrick D. Morris
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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,404,215 B1
APPLICATION NO.	: 13/417137
DATED	: March 26, 2013
INVENTOR(S)	: Scharschmidt et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page, in Item [54] "TITLE", and in the Specifications, column 1, line 2, insert --DRUGS-- after "NITROGEN SCAVENGING".

In the Claims

Claim 2, column 24, line 45, insert --c)-- before "administering the nitrogen".

Signed and Sealed this
Twenty-fifth Day of March, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court United States District Court, Eastern District of Texas on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
2:14-CV-384	4/23/2014	United States District Court, Eastern District of Texas

PLAINTIFF	DEFENDANT
Hyperion Therapeutics, Inc.	Par Pharmaceutical, Inc.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,404,215	3/26/2013	Hyperion Therapeutics, Inc.
2 8,642,012	2/4/2014	Hyperion Therapeutics, Inc.
3		
4		
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**