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FILING DATE: ***March 09, 2012***
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UNITED STATES PATENT AND TRADEMARK OFFICE
DEPARTMENT OF COMMERCE

Certified by

Michelle K. Lee

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

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)	
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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 1cfd2319bc7afa29a23939d99abdf96d286deb9e	no	2
Warnings:					
Information:					
2		US_Specification.pdf	407442 826a6226d6be4af33c5624c1715dd929e34b1e14	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 be0097bfb1b142993a8d25ef17815b6f7b9d1002	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	38065 662566fe500c17f8afc686d59086ba63210a15c6	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
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New International Application Filed with the USPTO as a Receiving Office
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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)
Approved for use through 07/31/2012. OMB 0651- 0031
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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.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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

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Application Number:	13417137
International Application Number:	
Confirmation Number:	6423
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First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Patrick D. Morris/Colleen Kirchner
Filer Authorized By:	Patrick D. Morris
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2		US_Specification.pdf	407442 826a6226d6be4af33c5624c1715dd929e34b1e14	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 be0097bfb1b142993a8d25ef17815b6f7b9d1002	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	38065 662566fe500c17f8afc686d59086ba63210a15c6	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	492771		

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National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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

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%.

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.

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).

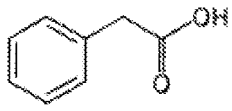
[0004] Hepatic encephalopathy (HE) refers to a spectrum of neurologic signs and symptoms believed to result from hyperammonemia, which frequently occur in subjects with cirrhosis or

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.

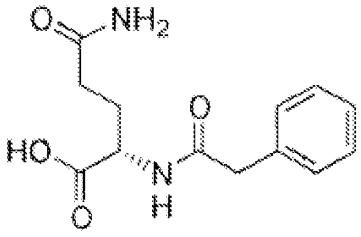
[0005] Subjects with nitrogen retention disorders whose ammonia levels and/or symptoms are not adequately controlled by dietary restriction of protein and/or dietary supplements are generally treated with nitrogen scavenging agents such as sodium phenylbutyrate (NaPBA, approved in the United States as 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 l.5 ULN, and a 93% chance (with a 95% confidence

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Figure 1

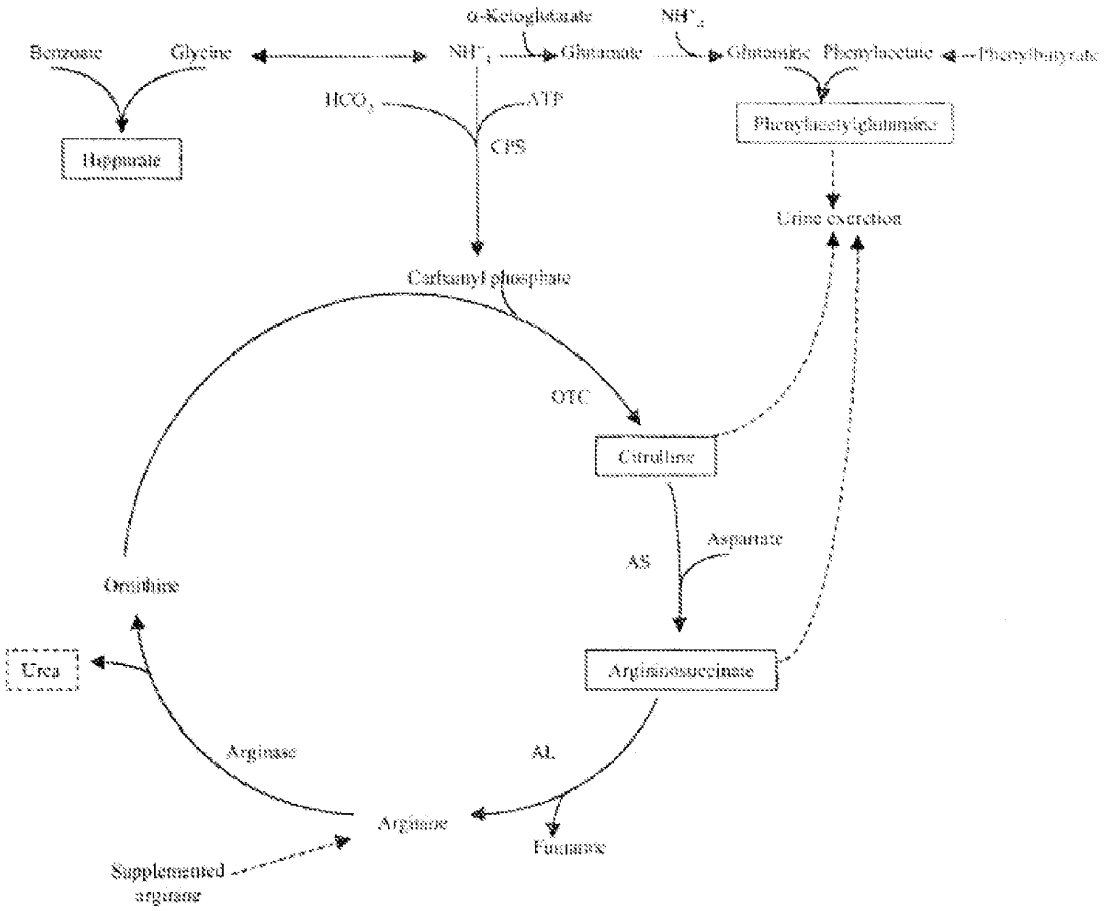


Figure 2

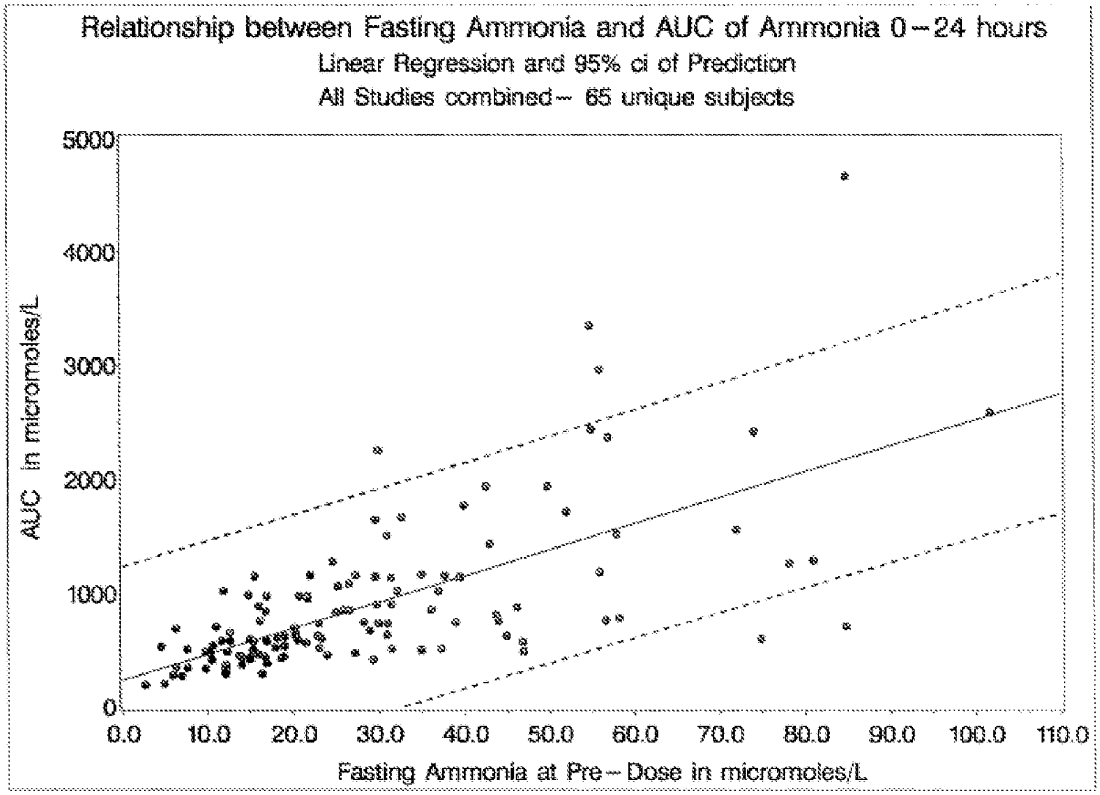
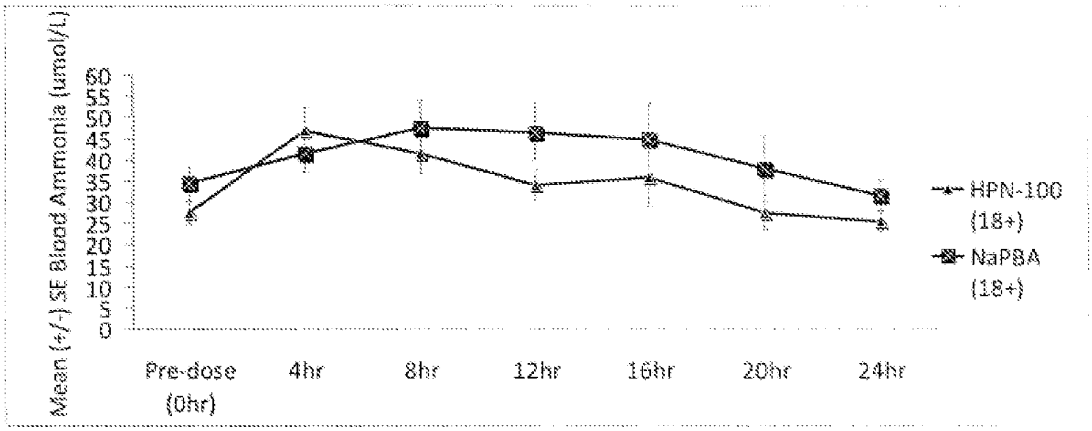


Figure 3

A.



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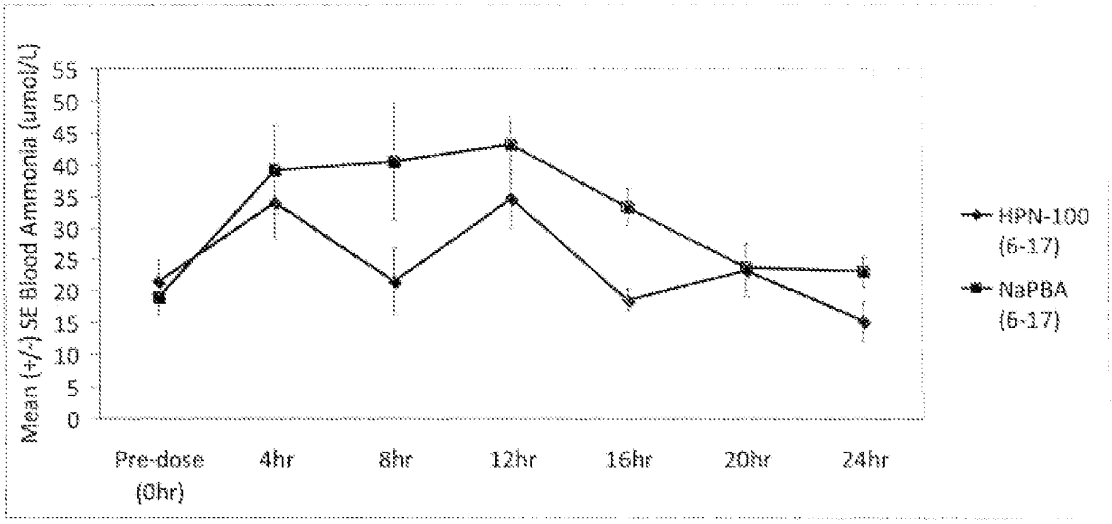

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First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
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OC000000053293071

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).

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				
6		3				
7		3				
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9		2				
10		3				
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50						
Total Indep	3		0		0	
Total Depend	24	↵	0	↵	0	↵
Total Claims	27		0		0	

	*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend
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100						

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($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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
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

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

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
Filed: March 9, 2012
Attorney Docket No. 79532.8003.US02

DECISION ON PETITION
TO MAKE SPECIAL UNDER
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

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 [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 [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	

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

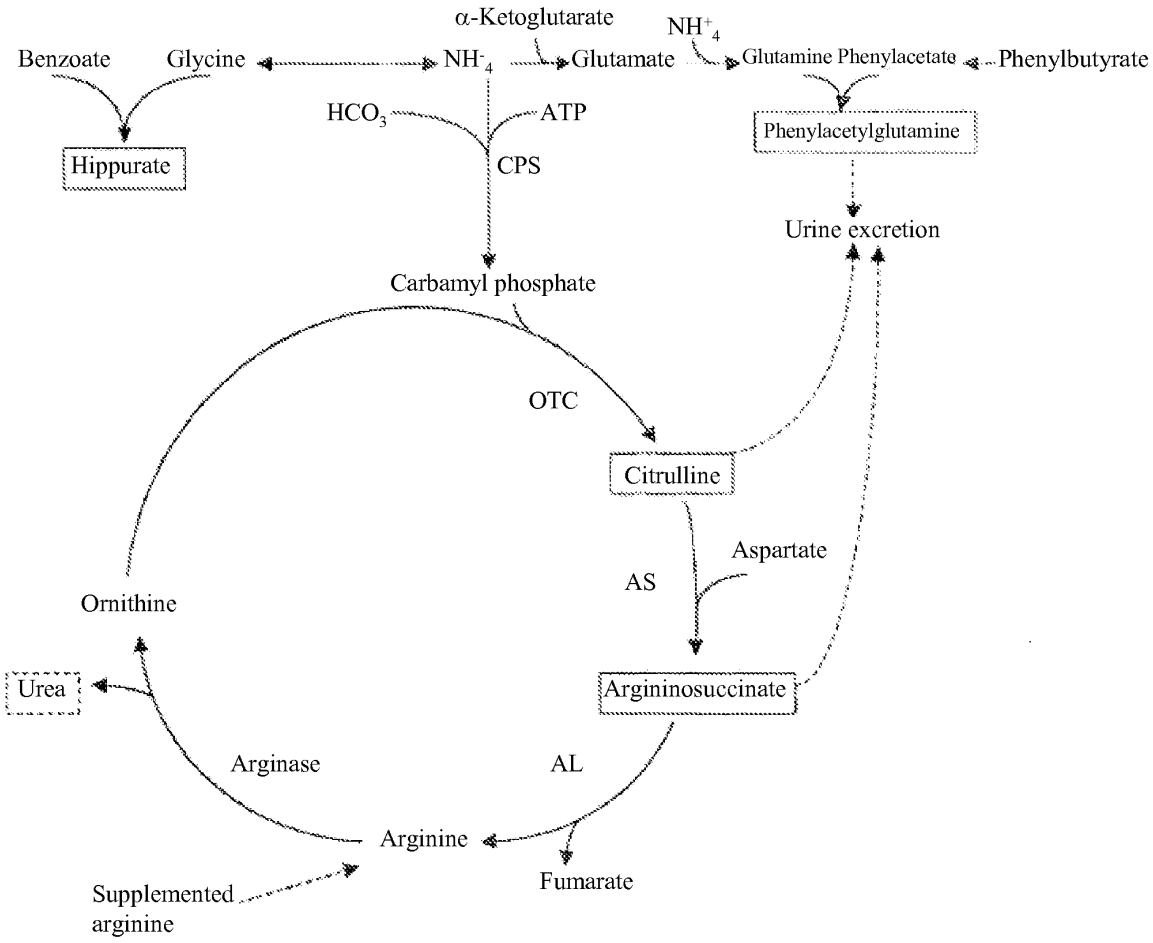

α-Ketoglutarate
NH^+_4
Benzoate
Glycine
NH^-_4
Glutamate
Glutamine
Phenylacetate
Phenylbutyrate
HCO_3
ATP
CPS
Hippurate
Phenylacetylglutamine
Urine excretion
Carbamyl phosphate
OTC
Citrulline
Aspartate
AS
Ornithine
Urea
Argininosuccinate
Arginase
AL
Arginine
Fumarate
Supplemented arginine

Figure 2

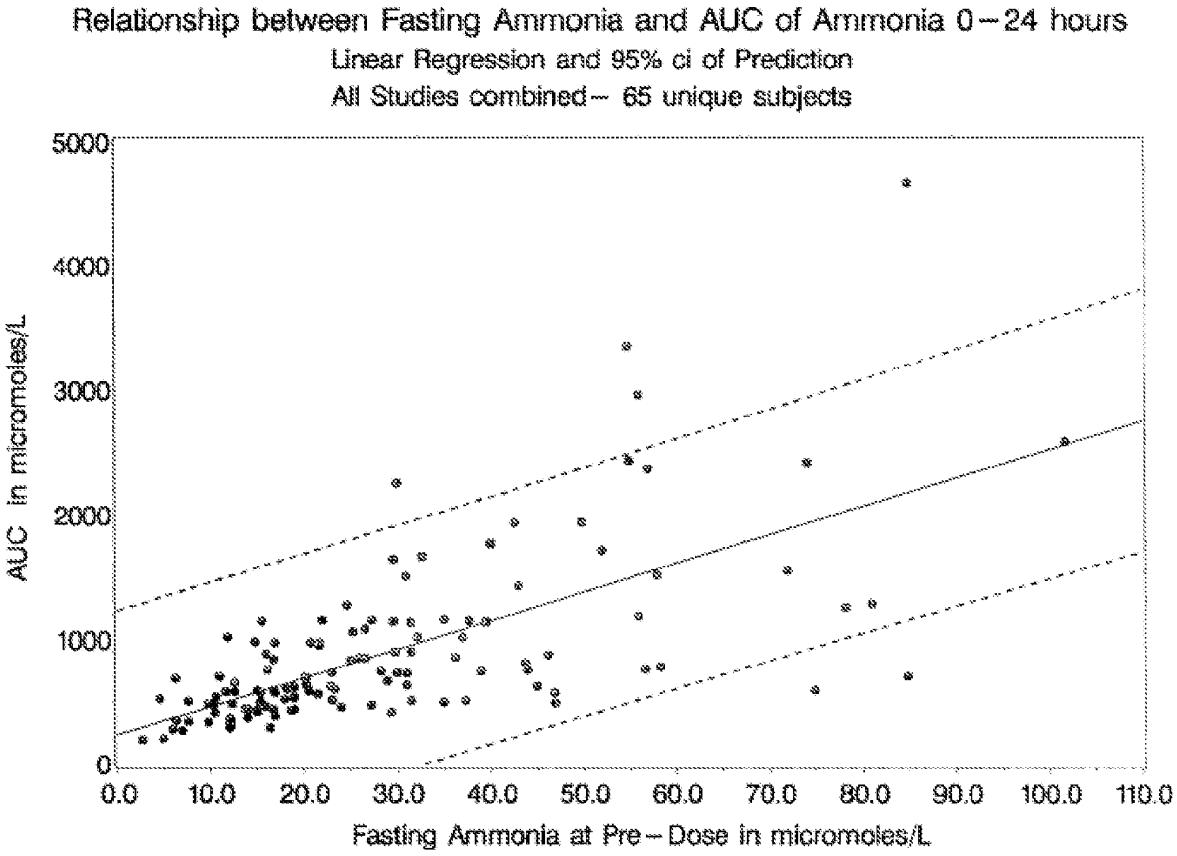
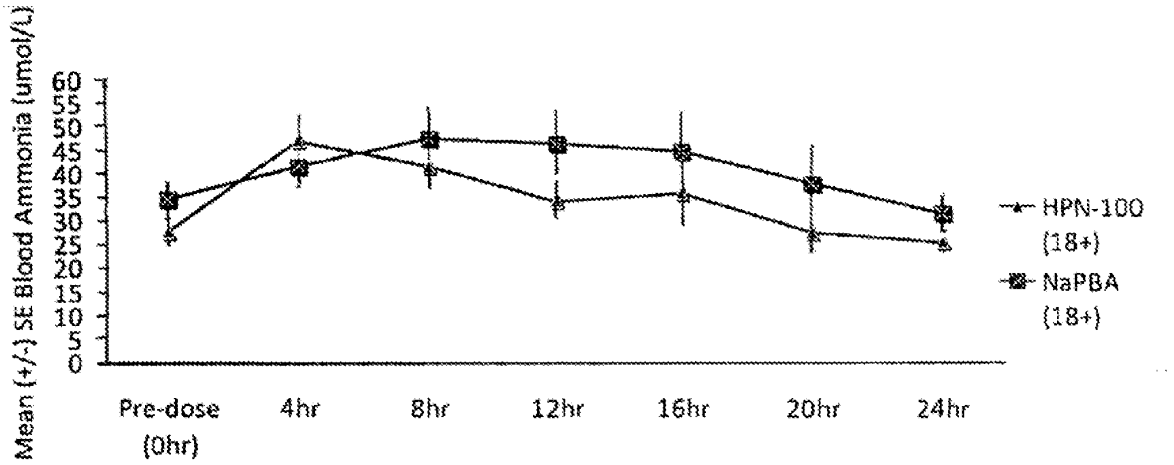
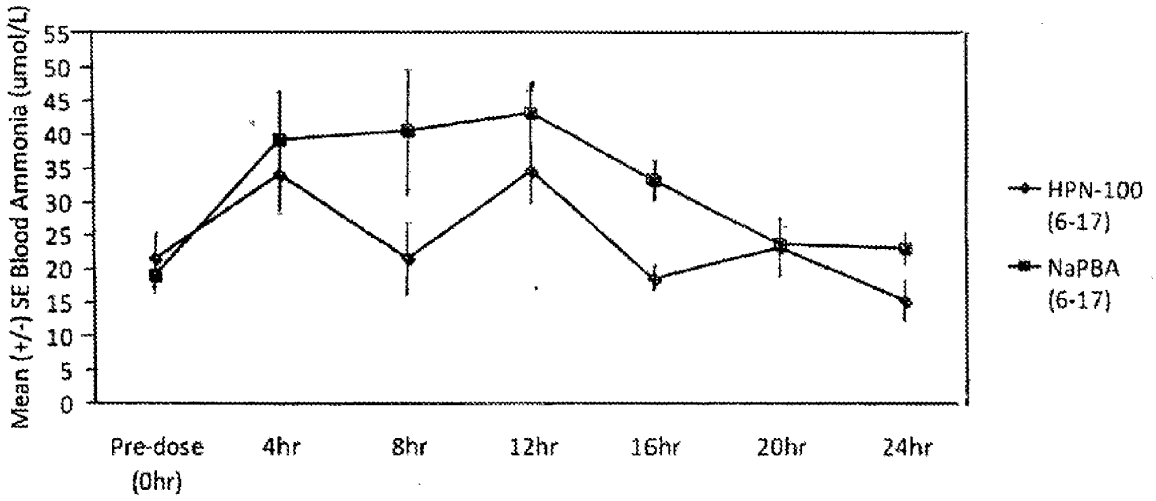

Relationship between Fasting Ammonia and AUC of Ammonia 0 – 24 hours
Linear Regression and 95% ci of Prediction
All Studies combined – 65 unique subjects
AUC in micromoles/L
5000
4000
3000
2000
1000
0
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
Fasting Ammonia at Pre – Dose in micromoles/L

Figure 3

A.


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

B.


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

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
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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.

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Respectfully submitted,
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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

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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:

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Longitudinal data analysis using generalized linear models

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SUMMARY

This paper proposes an extension of generalized linear models to the analysis of longitudinal data. We introduce a class of estimating equations that give consistent estimates of the regression parameters and of their variance under mild assumptions about the time dependence. The estimating equations are derived without specifying the joint distribution of a subject's observations yet they reduce to the score equations for multivariate Gaussian outcomes. Asymptotic theory is presented for the general class of estimators. Specific cases in which we assume independence, m-dependence and exchangeable correlation structures from each subject are discussed. Efficiency of the proposed estimators in two simple situations is considered. The approach is closely related to quasi-likelihood.

Some key words: Estimating equation; Generalized linear model; Longitudinal data; Quasi-likelihood; Repeated measures.

1. INTRODUCTION

Longitudinal data sets, comprised of an outcome variable, y_{it}, and a $p \times 1$ vector of covariates, x_{it}, observed at times $t = 1, \ldots, n_i$ for subjects $i = 1, \ldots, K$ arise often in applied sciences. Typically, the scientific interest is either in the pattern of change over time, e.g. growth, of the outcome measures or more simply in the dependence of the outcome on the covariates. In the latter case, the time dependence among repeated measurements for a subject is a nuisance. For example, the severity of respiratory disease along with the nutritional status, age, sex and family income of children might be observed once every three months for an 18 month period. The dependence of the outcome variable, severity of disease, on the covariates is of interest.

With a single observation for each subject ($n_i = 1$), a generalized linear model (McCullagh & Nelder, 1983) can be applied to obtain such a description for a variety of continuous or discrete outcome variables. With repeated observations, however, the correlation among values for a given subject must be taken into account. This paper presents an extension of generalized linear models to the analysis of longitudinal data when regression is the primary focus.

When the outcome variable is approximately Gaussian, statistical methods for longitudinal data are well developed, e.g. Laird & Ware (1982) and Ware (1985). For non-Gaussian outcomes, however, less development has taken place. For binary data, repeated measures models in which observations for a subject are assumed to have exchangeable correlations have been proposed by Ochi & Prentice (1984) using a probit link, by Stiratelli, Laird & Ware (1984) using a logit link and by Koch et al. (1977) using log linear models. Only the model proposed by Stiratelli, Laird & Ware allows for time-dependent covariates. Zeger, Liang & Self (1985) have proposed a first-order Markov

chain model for binary longitudinal data which, also, however, requires time independent covariates. One difficulty with the analysis of non-Gaussian longitudinal data is the lack of a rich class of models such as the multivariate Gaussian for the joint distribution of y_{it} $(t = 1, \ldots, n_i)$. Hence likelihood methods have not been available except in the few cases mentioned above.

The approach in this paper is to use a working generalized linear model for the marginal distribution of y_{it}. We do not specify a form for the joint distribution of the repeated measurements. Instead, we introduce estimating equations that give consistent estimates of the regression parameters and of their variances under weak assumptions about the joint distribution. We model the marginal rather than the conditional distribution given previous observations although the conditional approach may be more appropriate for some problems. The methods we propose reduce to maximum likelihood when the y_{it} are multivariate Gaussian.

The estimating equations introduced here are similar to those described by Jorgensen (1983) and by Morton (1981). However our problem differs from the one considered by Jorgensen in that the correlation parameters do not appear in the estimating equations in an additive way; it is different than the problem considered by Morton in that pivots cannot be used to remove the nuisance correlation parameters.

To establish notation, we let $Y_i = (y_{i1}, \ldots, y_{in_i})^T$ be the $n_i \times 1$ vector of outcome values and $X_i = (x_{i1}, \ldots, x_{in_i})^T$ be the $n_i \times p$ matrix of covariate values for the ith subject $(i = 1, \ldots, K)$. We assume that the marginal density of y_{it} is

$$f(y_{it}) = \exp\{(y_{it}\theta_{it} - a(\theta_{it}) + b(y_{it}))/\phi\}, \tag{1}$$

where $\theta_{it} = h(\eta_{it})$, $\eta_{it} = x_{it}\beta$. By this formulation, the first two moments of y_{it} are given by

$$E(y_{it}) = a'(\theta_{it}), \quad \text{var}(y_{it}) = a''(\theta_{it})/\phi. \tag{2}$$

When convenient to simplify notation, we let $n_i = n$ without loss of generality.

Section 2 presents the 'independence' estimating equation which arises by adopting the working assumption that repeated observations for a subject are independent. It leads to consistent estimates of β and of its variance given only that the regression model for $E(y)$ is correctly specified. Section 3 introduces and presents asymptotic theory for the 'generalized' estimating equation in which we borrow strength across subjects to estimate a 'working' correlation matrix and hence explicitly account for the time dependence to achieve greater asymptotic efficiency. In § 4, examples of specific models to be used in the analysis of longitudinal data are given. Section 5 considers questions of efficiency. The final section discusses several issues concerning the use of these estimating procedures.

2. Independence estimating equations

In this section, we present an estimator, $\hat{\beta}_I$, of β which arises under the working assumption that repeated observations from a subject are independent of one another. Under the independence working assumption, the score equations from a likelihood analysis have the form

$$U_I(\beta) = \sum_{i=1}^{K} X_i^T \Delta_i S_i = 0, \tag{3}$$

where $\Delta_i = \text{diag}\,(d\theta_{it}/d\eta_{it})$ is an $n \times n$ matrix and $S_i = Y_i - a_i'(\theta)$ is of order $n \times 1$ for the ith subject. The estimator $\hat{\beta}_I$ is defined as the solution of equation (3).

Define for each i the $n \times n$ diagonal matrix $A_i = \text{diag}\{a''(\theta_{it})\}$. Under mild regularity conditions we have the following theorem.

THEOREM 1. *The estimator $\hat{\beta}_I$ of β is consistent and $K^{\frac{1}{2}}(\hat{\beta}_I - \beta)$ is asymptotically multivariate Gaussian as $K \to \infty$ with zero mean and covariance matrix V_I given by*

$$V_I = \lim_{K\to\infty} K\left(\sum_{i=1}^{K} X_i^T \Delta_i A_i \Delta_i X_i\right)^{-1}\left(\sum_{i=1}^{K} X_i^T \Delta_i \text{cov}\,(Y_i)\,\Delta_i X_i\right)\left(\sum_{i=1}^{K} X_i^T \Delta_i A_i \Delta_i X_i\right)^{-1}$$

$$= \lim_{K\to\infty} K\{H_1(\beta)\}^{-1} H_2(\beta)\{H_1(\beta)\}^{-1}, \tag{4}$$

where the moment calculations for the Y_i's are taken with respect to the true underlying model.

The proof of the theorem is straightforward and is omitted. The variance of $\hat{\beta}_I$ given in Theorem 1 can be consistently estimated by

$$\{H_1(\hat{\beta}_I)\}^{-1}\left(\left[\sum_{i=1}^{K} X_i^T \Delta_i S_i S_i^T \Delta_i X_i\right]_{\hat{\beta}_I}\right)\{H_1(\hat{\beta}_I)\}^{-1}.$$

Note that the estimation of ϕ is unnecessary for estimating V_I even though the latter is a function of ϕ.

The estimator $\hat{\beta}_I$ has several advantages. It is easy to compute with existing software, e.g. GLIM (Baker & Nelder, 1978). Both $\hat{\beta}_I$ and $\text{var}\,(\hat{\beta}_I)$ are consistent given only a correct specification of the regression which is the principal interest. Note that this requires missing data to be missing completely at random in the sense of Rubin (1976). As discussed in §5, $\hat{\beta}_I$ can be shown to be reasonably efficient for a few simple designs. The principal disadvantage of $\hat{\beta}_I$ is that it may not have high efficiency in cases where the autocorrelation is large. The next section proposes a 'generalized' estimating equation that leads to estimators with higher efficiency.

3. GENERALIZED ESTIMATING EQUATIONS

3·1. *General*

In this section, we present a class of estimating equations which take the correlation into account to increase efficiency. The resulting estimators of β remain consistent. In addition, consistent variance estimates are available under the weak assumption that a weighted average of the estimated correlation matrices converges to a fixed matrix.

To begin, let $R(\alpha)$ be a $n \times n$ symmetric matrix which fulfills the requirement of being a correlation matrix, and let α be an $s \times 1$ vector which fully characterizes $R(\alpha)$. We refer to $R(\alpha)$ as a 'working' correlation matrix.

Define

$$V_i = A_i^{\frac{1}{2}} R(\alpha) A_i^{\frac{1}{2}}/\phi, \tag{5}$$

which will be equal to $\text{cov}\,(Y_i)$ if $R(\alpha)$ is indeed the true correlation matrix for the Y_i's.

We define the general estimating equations to be

$$\sum_{i=1}^{K} D_i^T V_i^{-1} S_i = 0, \tag{6}$$

where $D_i = \partial\{a_i'(\theta)\}/\partial\beta = A_i \Delta_i X_i$. Two remarks are worth mentioning. First, equation (6) reduces to the independence equations in §2 if we specify $R(\alpha)$ as the identity matrix.

Second, for each i, $U_i(\beta, \alpha) = D_i^T V_i^{-1} S_i$ is similar to the function derived from the quasi-likelihood approach advocated by Wedderburn (1974) and McCullagh (1983) except that the V_i's here are not only a function of β but of α as well. Equation (6) can be reexpressed as a function of β alone by first replacing α in (5) and (6) by $\hat{\alpha}(Y, \beta, \phi)$, a $K^{\frac{1}{2}}$-consistent estimator of α when β and ϕ are known, that is $\hat{\alpha}$ for which $K^{\frac{1}{2}}(\hat{\alpha} - \alpha) = O_p(1)$. Except for particular choices of R and $\hat{\alpha}$, the scale parameter ϕ will generally remain in (6). To complete the process, we replace ϕ by $\hat{\phi}(Y, \beta)$, a $K^{\frac{1}{2}}$-consistent estimator when β is known. Consequently, (6) has the form

$$\sum_{i=1}^{K} U_i\{\beta, \hat{\alpha}\{\beta, \hat{\phi}(\beta)\}\} = 0, \tag{7}$$

and $\hat{\beta}_G$ is defined to be the solution of equation (7). The next theorem states the large-sample property for $\hat{\beta}_G$.

THEOREM 2. *Under mild regularity conditions and given that:*
(i) $\hat{\alpha}$ *is* $K^{\frac{1}{2}}$*-consistent given* β *and* ϕ;
(ii) $\hat{\phi}$ *is* $K^{\frac{1}{2}}$*-consistent given* β; *and*
(iii) $|\partial \hat{\alpha}(\beta, \phi)/\partial \phi| \leqslant H(Y, \beta)$ *which is* $O_p(1)$,
then $K^{\frac{1}{2}}(\hat{\beta}_G - \beta)$ *is asymptotically multivariate Gaussian with zero mean and covariance matrix* V_G *given by*

$$V_G = \lim_{K \to \infty} K \left(\sum_{i=1}^{K} D_i^T V_i^{-1} D_i \right)^{-1} \left\{ \sum_{i=1}^{K} D_i^T V_i^{-1} \operatorname{cov}(Y_i) V_i^{-1} D_i \right\} \left(\sum_{i=1}^{K} D_i^T V_i^{-1} D_i \right)^{-1}.$$

A sketch of the proof is given in the Appendix. The variance estimate $\hat{V}_G$ of $\hat{\beta}_G$ can be obtained by replacing $\operatorname{cov}(Y_i)$ by $S_i S_i^T$ and β, ϕ, α by their estimates in the expression V_G. As in the independence case, the consistency of $\hat{\beta}_G$ and $\hat{V}_G$ depends only on the correct specification of the mean, not on the correct choice of R. This again requires that missing observations be missing completely at random (Rubin, 1976). Note that the asymptotic variance of $\hat{\beta}_G$ does not depend on choice of estimator for α and ϕ among those that are $K^{\frac{1}{2}}$-consistent. Analogous results are known for the Gaussian data case and in quasi-likelihood where the variance of the regression parameters does not depend on the choice of estimator of ϕ. In our problem, where the likelihood is not fully specified, the result follows from choosing estimating equations for β in which an individual's contribution, U_i, is a product of two terms: the first involving α but not the data, and the second independent of α and with expectation zero. Then $\sum E(\partial U_i/\partial \alpha)$ is $o_p(K)$ and $\operatorname{var}(\hat{\beta}_G)$ does not depend on $\hat{\alpha}$ or $\hat{\phi}$ as can be seen from the discussion in the Appendix.

3·2. *Connection with the Gauss–Newton method*

To compute $\hat{\beta}_G$, we iterate between a modified Fisher scoring for β and moment estimation of α and ϕ. Given current estimates $\hat{\alpha}$ and $\hat{\phi}$ of the nuisance parameters, we suggest the following modified iterative procedure for β:

$$\beta_{j+1} = \beta_j - \left\{ \sum_{i=1}^{K} D_i^T(\beta_j) \hat{V}_i^{-1}(\beta_j) D_i(\beta_j) \right\}^{-1} \left\{ \sum_{i=1}^{K} D_i^T(\beta_j) \hat{V}_i^{-1}(\beta_j) S_i(\beta_j) \right\}, \tag{8}$$

where $\hat{V}_i(\beta) = V_i[\beta, \hat{\alpha}\{\beta, \hat{\phi}(\beta)\}]$. This procedure can be viewed as a modification of Fisher's scoring method in that the limiting value of the expectation of the derivative of $\sum U_i[\beta, \hat{\alpha}\{\beta, \hat{\phi}(\beta)\}]$ is used for correction.

Now, define $D = (D_1^T, \ldots, D_K^T)^T$, $S = (S_1^T, \ldots, S_K^T)$ and let $\hat{V}$ be a $nK \times nK$ block diagonal matrix with $\hat{V}_i$'s as the diagonal elements. Define the modified dependent variable

$$Z = D\beta - S,$$

and then the iterative procedure (8) for calculating $\hat{\beta}_G$ is equivalent to performing an iteratively reweighted linear regression of Z on D with weight $\hat{V}^{-1}$.

3·3. *Estimators of α and ϕ*

At a given iteration the correlation parameters α and scale parameter ϕ can be estimated from the current Pearson residuals defined by

$$\hat{r}_{it} = \{y_{it} - a'(\hat{\theta}_{it})\}/\{a''(\hat{\theta}_{it})\}^{\frac{1}{2}},$$

where $\hat{\theta}_{it}$ depends upon the current value for β. We can estimate ϕ by

$$\hat{\phi}^{-1} = \sum_{i=1}^{K} \sum_{t=1}^{n_i} \hat{r}_{it}^2/(N-p),$$

where $N = \Sigma n_i$. This is the longitudinal analogue of the familiar Pearson statistic (Wedderburn, 1974; McCullagh, 1983). It is easily shown to be $K^{\frac{1}{2}}$-consistent given that the fourth moments of the y_{it}'s are finite. To estimate α consistently, we borrow strength over the K subjects. The specific estimator depends upon the choice of $R(\alpha)$. The general approach is to estimate α by a simple function of

$$\hat{R}_{uv} = \sum_{i=1}^{K} \hat{r}_{iu}\hat{r}_{iv}/(N-p).$$

Specific estimators are given in the next section.

Alternative estimators of ϕ such as one based upon the log likelihood described by McCullagh & Nelder (1983, p. 83) are available. Because we do not specify the entire joint distribution of Y_i, the analogous estimators for α are not available. Note, however, that the asymptotic distribution of $\hat{\beta}_G$ does not depend on the specific choice of α and ϕ among those that are $K^{\frac{1}{2}}$-consistent. The finite sample performance of $\hat{\beta}_G$ for a variety of α, ϕ estimators requires further study.

4. Examples

In this section several specific choices of $R(\alpha)$ are discussed. Each leads to a distinct analysis. The number of nuisance parameters and the estimator of α vary from case to case.

Example 1. Let $R(\alpha)$ be R_0, any given correlation matrix. When $R_0 = I$, the identity matrix, we obtain the independence estimating equation. However for any R_0, $\hat{\beta}_G$ and $\hat{V}_G$ will be consistent. Obviously, choosing R_0 closer to the true correlation gives increased efficiency. Note that for any specified R_0, no knowledge on ϕ is required in estimating β and var $(\hat{\beta}_G)$.

Example 2. Let $\alpha = (\alpha_1, \ldots, \alpha_{n-1})^T$, where $\alpha_t = \text{corr}(Y_{it}, Y_{i,t+1})$ for $t = 1, \ldots, n-1$. A natural estimator of α_t, given β and ϕ, is

$$\hat{\alpha}_t = \phi \sum_{i=1}^{K} \hat{r}_{it}\hat{r}_{i,t+1}/(K-p).$$

Now let $R(\alpha)$ be tridiagonal with $R_{t,t+1} = \alpha_t$. This is equivalent to the one-dependent model. An estimator of ϕ is unnecessary for calculating $\hat{\beta}_G$ and $\hat{V}_G$ when the α_t's above are used since the ϕ which appears in the formula for $\hat{\alpha}_t$ cancels in the calculation of V_t. As a special case, we can let $s = 1$ and $\alpha_t = \alpha$ $(t = 1, \ldots, n-1)$. Then the common α can be estimated by

$$\hat{\alpha} = \sum_{t=1}^{n-1} \hat{\alpha}_t/(n-1).$$

An extension to m-dependence is straightforward.

Example 3. Let $s = 1$ and assume that $\text{corr}(y_{it}, y_{it'}) = \alpha$ for all $t \neq t'$. This is the exchangeable correlation structure obtained from a random effects model with a random level for each subject, e.g. Laird & Ware (1982). Given ϕ, α can be estimated by

$$\hat{\alpha} = \phi \sum_{i=1}^{K} \sum_{t<t'} \hat{r}_{it}\hat{r}_{it'} \Big/ \left\{ \sum_{i=1}^{K} \tfrac{1}{2} n_i(n_i-1) - p \right\}.$$

As in Examples 1 and 2, ϕ need not be estimated to obtain $\hat{\beta}_G$ and V_G. Note that an arbitrary number of observations and observation times for each subject are possible with this assumption.

Example 4. Let $\text{corr}(y_{it}, y_{it'}) = \alpha^{|t-t'|}$. For y_{it} Gaussian, this is the correlation structure of the continuous time analogue of the first-order autoregressive process, AR-1 (Feller, 1971, p. 89). Since under this model, $E(\hat{r}_{it}\hat{r}_{it'}) \doteq \alpha^{|t-t'|}$, we can estimate α by the slope from the regression of $\log(\hat{r}_{it}\hat{r}_{it'})$ on $\log(|t-t'|)$. Note that an arbitrary number and spacing of observations can be accommodated with this working model. But $\hat{\phi}$ must be calculated in the determination of $\hat{\beta}_G$ and $\hat{V}_G$.

Example 5. Let $R(\alpha)$ be totally unspecified, that is $s = \frac{1}{2}n(n-1)$. Now R can be estimated by

$$\frac{\phi}{K} \sum_{i=1}^{K} A_i^{-\frac{1}{2}} S_i S_i^T A_i^{-\frac{1}{2}}. \tag{9}$$

Note that for this case, equations (6) and (9) together give the actual likelihood equations if the Y_i's follow a multivariate Gaussian distribution. Further, the asymptotic covariance, V_G, reduces to

$$\lim_{K\to\infty} \left\{ \sum_{i=1}^{K} D_i^T \text{cov}^{-1}(Y_i) D_i / K \right\}^{-1}$$

since R is the true correlation matrix. Again, no estimation of ϕ is required to obtain $\hat{\beta}_G$. However, this assumption is useful only with a small number of observation times.

5. Efficiency considerations

In this section, we consider two very simple data configurations and ask the following questions: (i) how much more efficient is $\hat{\beta}_G$ than $\hat{\beta}_I$, and (ii) how do $\hat{\beta}_G$ and $\hat{\beta}_I$ compare to the maximum likelihood estimator when further distributional assumptions on the Y_i's are made? To address the first question, consider the generalized linear model with natural link so that

$$\theta_{it} = x_{it}\beta \quad (t = 1, \ldots, 10),$$

We assume that each $X_i = (x_{i1}, \ldots, x_{i,10})'$ is generated from a distribution with mean $(0{\cdot}1, 0{\cdot}2, \ldots, 1{\cdot}0)'$ and finite covariance. Table 1 then gives the asymptotic relative efficiency of $\hat{\beta}_I$ and $\hat{\beta}_G$'s for three distinct correlation assumptions to the generalized estimator in which the correlation matrix is correctly specified. The correlation structures are one-dependent, exchangeable and first-order autoregressive, Examples 2, 3 and 4. The upper and lower entries are for $\alpha = 0{\cdot}3$ and $0{\cdot}7$ respectively.

Table 1. *Asymptotic relative efficiency of $\hat{\beta}_I$ and $\hat{\beta}_G$ to generalized estimator with correlation matrix correctly specified for $\eta_{it} = \beta_0 + \beta_1 t/10$. Here, $\beta_0 = \beta_1 = 1$, $n_i = 10$. For upper entry $\alpha = 0{\cdot}3$; lower entry $\alpha = 0{\cdot}7$*

	Working R			
True R	Independence	1-dependence	Exchangeable	AR-1
1-Dependence	0·97 0·74	1·0 1·0	0·97 0·74	0·99 0·81
Exchangeable	0·99 0·99	0·93 0·23	1·0 1·0	0·93 0·72
AR-1	0·97 0·88	0·99 0·75	0·97 0·88	1·0 1·0

There is little difference between $\hat{\beta}_I$ and the $\hat{\beta}_G$'s when the true correlation is moderate, $0{\cdot}3$ say. However, lower entries of Column 1 indicate that substantial improvement can be made by correctly specifying the correlation matrix when α is large. The efficiency of $\hat{\beta}_I$ relative to the $\hat{\beta}_G$ using the correct correlation matrix is lowest, 0·74, when R has the one-dependent form and highest, 0·99, when R has the exchangeable pattern. That $\hat{\beta}_I$ is efficient relative to $\hat{\beta}_G$ in the latter case is because $n_i = 10$ for all i so that the extra-binomial variation introduced by the exchangeable correlation is the same for all subjects and no misweighting occurs by ignoring it. If instead, we assume that n_i takes values from 1 to 8 with equal probability, the relative efficiency of $\hat{\beta}_I$ drops to 0·82. Note that the results in Table 1 hold regardless of the underlying marginal distribution.

To address the second question, we consider a two-sample configuration with binary outcomes. Subjects are in two groups, with marginal expectations satisfying $\text{logit}\{E(y_{it})\} = \beta_0 + \beta_1 x_i$, where $x_i = 0$ for Group 0, and 1 for Group 1. The repeated observations are assumed to come from a Markov chain of order 1 with first lag autocorrelation α. In Table 2, we compare the asymptotic relative efficiencies of $\hat{\beta}_I$ and

Table 2. *Asymptotic relative efficiency of $\hat{\beta}_I$ and $\hat{\beta}_G$ assuming* AR 1 *correlation structure to the maximum likelihood estimate for first-order Markov chain with $\theta_{it} = \beta_0 + \beta_1 x_i$, $x_i = 0$ for Group 0, $x_i = 1$ for Group 1. Here $\beta_0 = 0$, $\beta = 1$, and for upper entry $n_i = 10$, lower entry $n_i = 1, \ldots, 8$ with equal probabilities*

	Correlation, α						
	0·0	0·1	0·2	0·3	0·5	0·7	0·9
$\hat{\beta}_I$	1·0 1·0	1·0 1·0	0·99 0·98	0·97 0·96	0·94 0·92	0·91 0·86	0·92 0·81
$\hat{\beta}_G$ (AR 1)	1·0 1·0	1·0 1·0	0·99 0·99	0·99 0·99	0·98 0·98	0·97 0·98	0·98 0·99

β_G using the AR–1 correlation structure, Example 4, to the maximum likelihood estimator. For the upper entry, $n_i = 10$ for all i; for the lower, $n_i = 1$ to 8 with equal probability. The results indicate that both β_I and β_G are highly efficient for smaller α. As α increases, β_G retains nearly full efficiency while β_I does not. The contrast between β_I and β_G is strongest for the unequal sample size case.

6. DISCUSSION

The analysis of non-Gaussian longitudinal data is difficult partly because few models for the joint distribution of the repeated observations for a subject are available. On the other hand, longitudinal data offer the advantage that data from distinct subjects are independent. The methods we propose avoid the need for multivariate distributions by only assuming a functional form for the marginal distribution at each time. The covariance structure across time is treated as a nuisance. We rely, however, on the independence across subjects to estimate consistently the variance of the proposed estimators even when the assumed correlation is incorrect, as we expect it often will be.

Modelling the marginal expectation and treating the correlation as a nuisance may be less appropriate when the time course of the outcome for each subject, e.g. growth, is of primary interest or when the correlation itself has scientific relevance. The random effects model for binary data discussed by Stiratelli, Laird & Ware (1984) can be extended to the generalized linear model family and is more appropriate for the study of growth. When the time dependence is central, models for the conditional distribution of y_t given $y_{t-1}, y_{t-2}, \cdots, y_1$ may be more appropriate. Cox (1970, p. 72) has proposed such a model for binary outcomes. Korn & Whittemore (1979) have applied this model to air pollution data.

The examples in §4 provide several alternative methods for analysing longitudinal data sets. The method in Example 1, which includes the independence estimating equation as a special case, requires the fewest assumptions. Only the regression specification must be correct to obtain consistent estimates of β and var $(\hat{\beta})$. In §5, the independence estimator was shown to have high efficiency when the correlation is moderate in a simple situation with binary outcomes, Table 2. We believe that it may be less efficient in more realistic situations with more heterogeneity among both the X_i's and n_i's. Further study is needed.

Among the remaining methods implied by the generalized estimating equation, allowing R to have $\frac{1}{2}n(n-1)$ parameters, Example 5 gives the most efficient estimator. This approach, however, is only useful when there are few observation times. The remaining estimators will be as efficient only if the true correlation matrix can be expressed in terms of the chosen $R(\alpha)$ for some α. In particular, all generalized estimating equation estimators will be efficient if observations for a subject are independent. Note that each estimator and its variance will be consistent as long as α and ϕ can be estimated consistently for any correlation.

Missing data are common in some longitudinal studies. For β_G and V_G to be consistent even when R is misspecified, we require that data be missing completely at random (Rubin, 1976). That is, whether an observation is missing cannot depend on previous outcomes. Intuitively, we should not expect to handle complicated missing value patterns unless our working model is correct. When R is the true correlation, the missing completely at random assumption can be unnecessary. For Gaussian outcomes, the missing data pattern can depend arbitrarily on past observations and consistency is

retained. For binary outcomes, the pattern can depend on any single previous outcome.

If the elements of R are proportional to those of α, then the scale parameter, ϕ, does not have to be determined as a step in solving the general estimating equation. This was the case for all examples above except 4. Note that ϕ also is eliminated from the estimation of β in quasi-likelihood methods (Wedderburn, 1974). In addition, the variance of $\hat{\beta}_G$ does not depend on the choice of estimator of the nuisance parameters, α and ϕ among those that are $K^{\frac{1}{2}}$-consistent. This is also the case in quasi-likelihood where the only nuisance paranieter is ϕ. The estimating equations described in this paper can be thought of as an extension of quasi-likelihood to the case where the second moment cannot be fully specified in terms of the expectation but rather additional correlation parameters must be estimated. It is the independence across subjects that allowe us to consistently estimate these nuisance parameters where this could not be done otherwise.

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Appendix

Proof of Theorem 2

Write $\alpha^*(\beta) = \hat{\alpha}\{\beta, \hat{\phi}(\beta)\}$ and under some regularity conditions $K^{\frac{1}{2}}(\hat{\beta}_G - \beta)$ can be approximated by

$$\left[\sum_{i=1}^{K} -\frac{\delta}{\delta\beta} U_i\{\beta, \alpha^*(\beta)\}/K\right]^{-1}\left[\sum_{i=1}^{K} U_i\{\beta, \alpha^*(\beta)\}/K^{\frac{1}{2}}\right],$$

where

$$\begin{aligned}\delta U_i\{\beta, \alpha^*(\beta)\}/\delta\beta &= \partial U_i\{\beta, \alpha^*(\beta)\}/\partial\beta + \{\partial U_i\{\beta, \alpha^*(\beta)\}/\partial\alpha^*\}\{\partial\alpha^*(\beta)/\partial\beta\} \\ &= A_i + B_i C, \end{aligned} \tag{A1}$$

Let β be fixed and Taylor expansion gives

$$\begin{aligned}\frac{\Sigma\, U_i\{\beta, \alpha^*(\beta)\}}{K^{\frac{1}{2}}} &= \frac{\Sigma\, U_i(\beta, \alpha)}{K^{\frac{1}{2}}} + \frac{\Sigma\, \partial/\partial\alpha\, U_i(\beta, \alpha)}{K} K^{\frac{1}{2}}(\alpha^* - \alpha) + o_p(1) \\ &= A^* + B^* C^* + o_p(1), \end{aligned} \tag{A2}$$

where the sums are over $i = 1, \ldots, K$. Now, $B^* = o_p(1)$, since $\partial U_i(\beta, \alpha)/\partial\alpha$ are linear functions of S_i's whose means are zero, and conditions (i) to (iii) give

$$\begin{aligned} C^* &= K^{\frac{1}{2}}[\hat{\alpha}\{\beta, \hat{\phi}(\beta)\} - \hat{\alpha}(\beta, \phi) + \hat{\alpha}(\beta, \phi) - \alpha] \\ &= K^{\frac{1}{2}}\left\{\frac{\partial\hat{\alpha}}{\partial\phi}(\beta, \phi^*)(\hat{\phi} - \phi) + \hat{\alpha}(\beta, \phi) - \alpha\right\} = O_p(1). \end{aligned}$$

Consequently, $\Sigma\, U_i\{\beta, \alpha^*(\beta)\}/K^{\frac{1}{2}}$ is asymptotically equivalent to A^* whose asymptotic distribution is multivariate Gaussian with zero mean and covariance matrix

$$\lim_{K\to\infty}\left\{\sum_{i=1}^{K} D_i^{\mathrm{T}} V_i^{-1}\,\mathrm{cov}\,(Y_i)\, V_i^{-1} D_i/K\right\}.$$

Finally, it is easy to see that $\Sigma\, B_i = o_p(K)$, $C = O_p(1)$ and that $\Sigma\, A_i/K$ converges as $K \to \infty$ to $-\Sigma\, D_i^{\mathrm{T}} V_i^{-1} D_i/K$. This completes the proof.

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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	6	of	10	Attorney Docket No.	79532.8003.US02

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	C43	JOHN, BA et al. (March 2009). "The Disposition of HPN-100, A Novel Pharmaceutical Under Development for Potential Treatment of Hyperammonemia, in Cynomologus Monkeys," abstract presented at ACMG 2009, one page.	
	C44	JOHN, BA et al. (March 2009). "The Disposition of HPN-100, A Novel Pharmaceutical Under Development for Potential Treatment of Hyperammonemia, in Cynomolgus Monkeys," ACMG 2009 ADME, poster, two pages.	
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	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.	
	C47	LEE, B. et al. (August 2009). "Dosing and Therapeutic Monitoring of Ammona Scavenging Drugs and Urinary Phenylacetylglutamine (PAGN) as a Biomarker: Lessons From a Phase 2 Comparison of a Novel Ammonia Scavenging Agent with Sodium Phenyl butyrate (NAPBA)," presented at ICIEM 2009, San Diego, CA, poster, one page.	
	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.	
	C49	LEE, B. et al. (March 2009). "Phase 2 Study of A Novel Ammonia Scavenging Agent in Adults with Urea Cycle Disorders (UCDs)," presented at ACMG 2009, seventeen pages.	

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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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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.

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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

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PERKINS COIE LLP
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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

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

CONFIRMATION NO. 6423

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

POA ACCEPTANCE LETTER

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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

ORIGINAL ARTICLE

Survival after Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders

Gregory M. Enns, M.B., Ch.B., Susan A. Berry, M.D., Gerard T. Berry, M.D., William J. Rhead, M.D., Ph.D., Saul W. Brusilow, M.D., and Ada Hamosh, M.D., M.P.H.

ABSTRACT

BACKGROUND

The combination of intravenous sodium phenylacetate and sodium benzoate has been shown to lower plasma ammonium levels and improve survival in small cohorts of patients with historically lethal urea-cycle enzyme defects.

METHODS

We report the results of a 25-year, open-label, uncontrolled study of sodium phenylacetate and sodium benzoate therapy (Ammonul, Ucyclyd Pharma) in 299 patients with urea-cycle disorders in whom there were 1181 episodes of acute hyperammonemia.

RESULTS

Overall survival was 84% (250 of 299 patients). Ninety-six percent of the patients survived episodes of hyperammonemia (1132 of 1181 episodes). Patients over 30 days of age were more likely than neonates to survive an episode (98% vs. 73%, P<0.001). Patients 12 or more years of age (93 patients), who had 437 episodes, were more likely than all younger patients to survive (99%, P<0.001). Eighty-one percent of patients who were comatose at admission survived. Patients less than 30 days of age with a peak ammonium level above 1000 μmol per liter (1804 μg per deciliter) were least likely to survive a hyperammonemic episode (38%, P<0.001). Dialysis was also used in 56 neonates during 60% of episodes and in 80 patients 30 days of age or older during 7% of episodes.

CONCLUSIONS

Prompt recognition of a urea-cycle disorder and treatment with both sodium phenylacetate and sodium benzoate, in conjunction with other therapies, such as intravenous arginine hydrochloride and the provision of adequate calories to prevent catabolism, effectively lower plasma ammonium levels and result in survival in the majority of patients. Hemodialysis may also be needed to control hyperammonemia, especially in neonates and older patients who do not have a response to intravenous sodium phenylacetate and sodium benzoate.

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Urea-cycle disorders are inborn errors of metabolism that are characterized by episodic, life-threatening hyperammonemia resulting from partial or complete inactivity of enzymes responsible for eliminating nitrogenous waste. Historically, mortality and morbidity have been very high, and survivors commonly have had devastating neurologic sequelae.[1] Initial efforts to remove accumulated ammonium in patients with hyperammonemic encephalopathy included lactulose therapy,[2] exchange transfusion,[3,4] peritoneal dialysis,[4] hemodialysis,[5] and supplementation with nitrogen-free analogues of essential amino acids.[6] These treatments prolonged survival in some patients, but the overall efficacy was disappointing — and mortality and morbidity remained high.

Current therapeutic strategies include reducing the production of nitrogenous waste with the use of a low-protein diet and preventing endogenous catabolism through the provision of adequate nutrition. In addition, exploitation of alternative pathways for excretion of waste nitrogen has played a critical role in the management of urea-cycle disorders since Brusilow and colleagues first suggested using endogenous biosynthetic pathways to eliminate non–urea-waste nitrogen as a substitute for defective urea synthesis.[7] In theory, the total body load of nitrogen can be decreased, despite abnormal urea-cycle functioning, by promoting the synthesis of non-urea nitrogen-containing metabolites that have high excretion rates or rates that may be augmented.[7-11] The first successful demonstration of this concept was the use of arginine supplementation for the treatment of argininosuccinate lyase deficiency.[9]

An open-label, uncontrolled, multicenter study of intravenous sodium phenylacetate and sodium benzoate combined (Ammonul, Ucyclyd Pharma) as an emergency treatment for hyperammonemia in patients with urea-cycle disorders was conducted in the United States and Canada from 1980 to 2005. The primary purpose of the study was to determine whether treatment with sodium phenylacetate and sodium benzoate reduced mortality due to acute hyperammonemia, as compared with historical data.

METHODS

STUDY DESIGN

We conducted an open-label, uncontrolled, nonrandomized study at 118 hospitals in the United States and Canada between August 1980 and March 2005. The patients included in the study were hospitalized because of hyperammonemia resulting from a urea-cycle defect. A total of 299 patients with urea-cycle disorders and 1181 episodes of hyperammonemia were included. Four patients for whom demographic data were incomplete were excluded. To enroll a patient, the investigator contacted one of the authors (S.W.B.) at Johns Hopkins School of Medicine (from 1982 through 1996), or Ucyclyd Pharma (from 1997 through 2005), which supplied the study drug and case-report forms. The institutional review board at each participating institution approved the study. Written informed consent was obtained from the parents or legal guardians of children enrolled and from adult patients.

TREATMENT

Infants and children (weighing up to 20 kg [44 lb]) who had carbamyl phosphate synthetase deficiency, ornithine transcarbamylase deficiency, or argininosuccinate synthetase deficiency were treated with an initial (loading) dose of sodium phenylacetate (250 mg per kilogram of body weight) and sodium benzoate (250 mg per kilogram) administered intravenously over a period of 90 to 120 minutes. Older children (weighing more than 20 kg) and adults were treated with sodium phenylacetate and sodium benzoate, 5.5 g per square meter of body-surface area, as an intravenous loading dose over a period of 90 to 120 minutes. After the loading dose, maintenance infusions of the same dose were continued over 24 hours until the patient no longer had hyperammonemia and oral therapy could be tolerated. Among the factors limiting tolerance were vomiting, decreased intestinal motility, and the presence of umbilical catheters. Intravenous ondansetron (Zofran, GlaxoSmithKline) (0.15 mg per kilogram) was used in some patients to prevent or treat hyperemesis. Guidelines for administering sodium phenylacetate and sodium benzoate were not available for the treatment of argininosuccinate lyase deficiency or arginase deficiency. Loading and maintenance infusions also contained arginine hydrochloride (210 mg per kilogram for patients with ornithine transcarbamylase deficiency or carbamyl phosphate synthetase deficiency, and 630 mg per kilogram for patients with argininosuccinate synthetase deficiency or argininosuccinate lyase deficiency). Although a dialysis protocol was not used, dialysis, as noted below, was recommended for any neonate with hyperammonemic encephalopathy or any oth-

er patient in whom the ammonium level did not decrease substantially within 8 hours after administration of the loading infusion. Not all investigators followed these treatment guidelines precisely.

ASSESSMENT

The primary end point was survival of the episode of hyperammonemia. When a patient died, the investigator was asked to identify the primary and secondary causes of the death and to assess the relationship of the death to the primary disease and to the study drug. Plasma ammonium data were collected and analyzed according to a schedule determined by each investigator.

STATISTICAL ANALYSIS

Data were summarized with the use of descriptive statistics. An episode was defined as a single hospitalization for hyperammonemia. For comparisons according to age and diagnosis, P values for survival were calculated with the use of Fisher's exact test for each category, as compared with all other categories. For the comparison according to peak ammonium level, P values for survival were calculated with the use of Fisher's exact test for each category of ammonium level, as compared with all categories of lower ammonium levels.

Outcome at discharge (survival vs. death) was also compared according to coma status at admission. Separate analyses according to coma status at admission were performed for all episodes and for different age groups and enzyme deficiency. P values were calculated with the use of the McNemar test for the comparison between outcome at discharge (alert vs. comatose vs. deceased) and coma status at admission (coma vs. no coma).

RESULTS

SURVIVAL

Over the 25 years of the study, 299 patients with urea-cycle disorders were treated with sodium phenylacetate and sodium benzoate for a total of 1181 episodes of hyperammonemia. The patients included 93 neonates (94 episodes) and 237 patients older than 30 days of age (1087 episodes) (Table 1 and Fig. 1). Thirty-one patients were treated both as neonates and as older patients and thus were included in the totals for both groups. The mean (±SD) number of episodes per patient was 3.3±6.3 (range, 1 to 79). Dialysis (including standard hemodialysis, various combinations of arteriovenous and venovenous hemofiltration, and peritoneal dialysis) was used during 136 of the 1181 episodes (12%) and in 105 of 299 patients (35%). Dialysis was used more commonly in neonates (56 neonates, 60% of episodes) than in older patients (80 patients, 7% of episodes). Peritoneal dialysis with no other form of dialysis was used in six neonates and was used in combination with hemodialysis, a form of hemofiltration, or both in four neonates and two older patients. Overall the rate of survival (defined as survival of all known episodes for each patient) was 84% (250 of 299 patients) (Table 1). The survival rate for hyperammonemic episodes was 96% (1132 of 1181 episodes). Patients more than 30 days of age were more likely to survive an episode of hyperammonemia than were neonates (survival rates, 98% and 73%, respectively; P<0.001). Patients more than 12 years of age (93 patients, 437 episodes) were most likely to survive an episode of hyperammonemia (survival rate, 99%; P<0.001, as compared with all other age groups) (Table 2).

The survival rate for episodes of hyperammonemia was significantly lower among male patients with ornithine transcarbamylase deficiency (91%) than among female patients with the same deficiency (98%) and among patients with a deficiency of carbamyl phosphate synthetase, argininosuccinate synthetase, or argininosuccinate lyase (P<0.001) (Table 2). The survival rate appeared to be lower among patients with arginase deficiency (80%) than among those with a deficiency of ornithine transcarbamylase, carbamyl phosphate synthetase, argininosuccinate synthetase, or argininosuccinate lyase but the difference did not reach statistical significance (Table 2); there were only five episodes reported in patients with arginase deficiency. Indeed, the single patient with arginase deficiency who died had neonatal sepsis and relatively mild hyperammonemia (<200 μmol per liter [361 μg per deciliter]).

Thirteen of the 49 patients who died received sodium phenylacetate and sodium benzoate in amounts that were greater than the recommended doses. Of these 13 patients, 7 received a bolus dose of sodium phenylacetate and sodium benzoate ranging from 370 to 620 mg per kilogram. One patient was given a bolus dose of sodium phenylacetate and sodium benzoate approximately 9 times higher than that recommended (2310 mg of each medication per kilogram). In addition, seven patients were given multiple (range, one to

Table 1. **Survival According to Diagnosis and Age at Presentation.**

Variable	Carbamyl Phosphate Synthetase Deficiency	Ornithine Transcarbamylase Deficiency		Argininosuccinate Synthetase Deficiency	Argininosuccinate Lyase Deficiency	Overall Survival*
	All Patients (N=41)	Male Patients (N=86)	Female Patients (N=78)	All Patients (N=80)	All Patients (N=11)	All Patients (N=299)
	number/total number (percent)					
Survived first known episode	37/41 (90)	66/86 (77)	70/78 (90)	75/80 (94)	10/11 (91)	260/299 (87)
Age ≤30 days	9/12 (75)	24/40 (60)	2/3 (67)	28/32 (88)	5/5 (100)	68/93 (73)
Age >30 days	28/29 (97)	42/46 (91)	69/75 (92)	47/48 (98)	5/6 (83)	193/206 (94)
Survived all known episodes	34/41 (83)	61/86 (71)	69/78 (88)	73/80 (91)	10/11 (91)	250/299 (84)
Neonatal onset (age ≤30 days)	8/12 (67)	21/40 (53)	2/3 (67)	27/32 (84)	5/5 (100)	63/93 (68)
Presumed late onset (age >30 days)	27/29 (93)	40/46 (87)	68/75 (91)	46/48 (96)	5/6 (83)	188/206 (91)

* Three patients with arginase deficiency were treated with sodium phenylacetate and sodium benzoate; one had neonatal onset of the disease and died during the first episode, and two had a total of four episodes and survived. Because ornithine transcarbamylase deficiency is an X-linked disorder, male patients typically have a more severe clinical phenotype than do female patients, so for this disorder a distinction on the basis of sex was made.

seven) additional bolus infusions of sodium phenylacetate and sodium benzoate after administration of the initial bolus. Two other male patients with ornithine transcarbamylase deficiency were given high maintenance doses of each medication (an 18-year-old was given 6.25 g per square meter of body-surface area over a 23-hour period and a neonate 4380 mg per kilogram over a 25-hour period).

The majority of patients had adverse events during treatment for hyperammonemia; disorders of the metabolic system, the nervous system, and the respiratory system were most commonly reported (Table 3). In the 49 patients who died, coexisting conditions were common and included seizures (19 patients), infection (18), cerebral edema or increased intracranial pressure (16), disseminated intravascular coagulation (9), kidney failure (6), multiorgan system failure (5), and cerebral hemorrhage (5).

SURVIVAL AND COMA AT ADMISSION

Among 209 patients, there were 1020 episodes of hyperammonemia without coma at the time of admission. When coma was not present on admission, in the overwhelming majority (992) of these episodes (97%), coma was also absent at the time of discharge. However, 22 episodes in which coma was absent on admission resulted in death (2%), and in 6 episodes (<1%) coma persisted at the time of discharge (five patients with coma at discharge were transferred to other hospitals for treatment with dialysis, and one was transferred to another center for liver transplantation). Among 82 patients, there were 120 episodes in which the patients were comatose on admission. Overall, when patients were comatose on admission, no coma was present at the time of discharge (97 episodes, 81%); 23 episodes in which the patients were comatose at admission resulted in death (19%) (Table 2).

The survival rate for hyperammonemic episodes was significantly lower among patients who were comatose at admission, both among neonates ($P=0.002$) and among older patients ($P<0.001$). Children 2 to 12 years of age who were comatose at admission had a relatively lower rate of survival of a hyperammonemic episode (79%) than those in other groups over 30 days of age. The survival rate was lowest among male patients with ornithine transcarbamylase deficiency who were comatose at admission (68%) (Table 2).

SURVIVAL AND PEAK AMMONIUM LEVEL

Survival was significantly improved for patients who had hyperammonemic episodes with a peak plasma ammonium level of 500 μmol per liter (902 μg per deciliter) or less than among those with higher peak ammonium levels ($P<0.001$). Patients less than 30 days of age with a peak ammonium

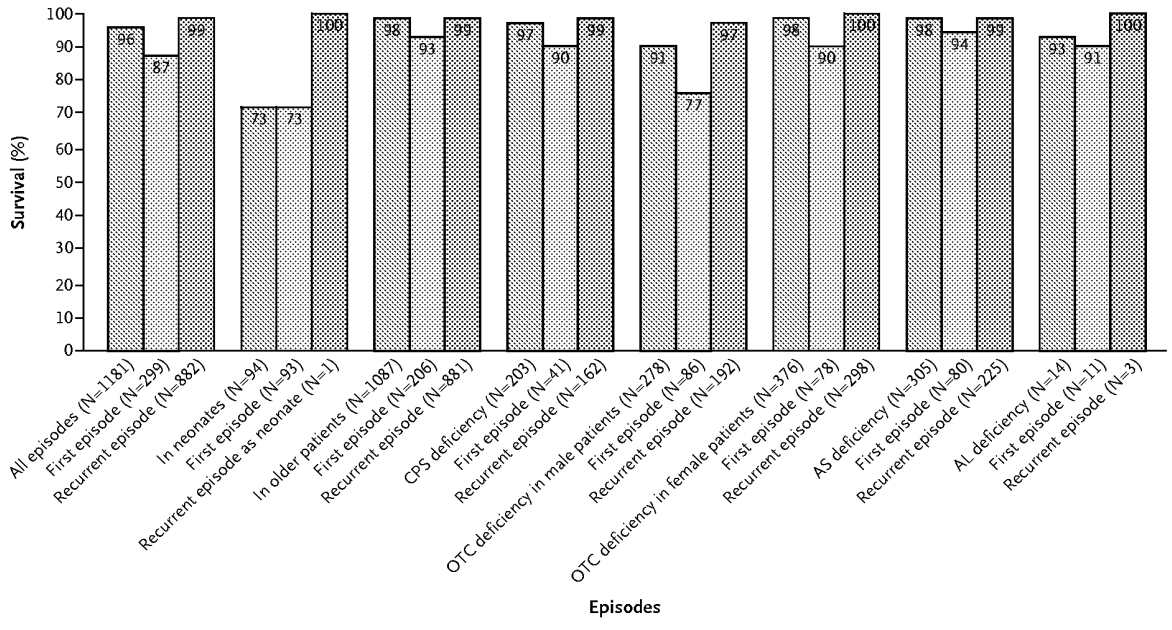

Figure 1. **Survival of Episodes of Hyperammonemia, According to Age, Diagnosis, and First Episode versus Recurrent Episodes.**
Because ornithine transcarbamylase (OTC) deficiency is an X-linked disorder, male patients typically have a more severe clinical phenotype than do female patients, and for that reason a distinction on the basis of sex was made. CPS denotes carbamyl phosphate synthetase, and AS argininosuccinate synthetase.

level greater than 1000 μmol per liter (1804 μg per deciliter) were least likely to survive a hyperammonemic episode (survival, 38%; P<0.001) (Table 4 and Fig. 2).

CHANGES IN AMMONIUM LEVELS

Plasma ammonium levels decreased substantially in most patients after therapy with the use of the intravenous treatment protocol (alternative-pathway therapy for nitrogen excretion). For all episodes in which both a baseline ammonium level (the last value recorded before treatment with sodium phenylacetate and sodium benzoate plus arginine hydrochloride was begun) and the level measured after treatment was initiated were known (582 patients), the median ammonium level fell from 185 μmol per liter (334 μg per deciliter) to 36 μmol per liter (65 μg per deciliter) at the final assessment (–79% change from baseline). Plasma ammonium levels decreased substantially in both neonates and older patients, although the median ammonium levels were markedly higher in neonates than in older patients at baseline. Among patients who died, median ammonium levels were similar at baseline and at the final assessment (334 and 364 μmol per liter [603 and 657 μg per deciliter] among neonates and 168 and 116 μmol per liter [303 and 209 μg per deciliter] among older patients, respectively). Median ammonium levels decreased substantially in patients who survived (from 374 to 24 μmol per liter [675 to 43 μg per deciliter] among neonates and 179 to 36 μmol per liter [323 to 65 μg per deciliter] among older patients).

DISCUSSION

Historically, survival among patients with urea-cycle disorders was poor after episodes of hyperammonemia; most children with a severe enzyme deficiency died as neonates — and few survived infancy.[1,12,13] In 1979, Brusilow et al. hypothesized that hyperammonemic coma caused by urea-cycle disorders might be treated with a combination of sodium phenylacetate and sodium benzoate.[7] The potential of the use of alternative pathways of nitrogen excretion to treat hyperammonemic coma was demonstrated soon thereafter; the administration of sodium benzoate either orally or intravenously in four patients

Table 2. **Outcomes of 1181 Episodes of Hyperammonemia, According to Age, Diagnosis, and Coma Status at Admission.***

Variable	Status at Discharge			P Value†	Survival	P Value‡
	Alert	Comatose	Dead			
	no. of patients/total no. (%)				*no. of patients/ total no. (%)*	
All episodes				<0.001	1132/1181 (96)	
Coma at admission	97/120 (81)	0	23/120 (19)			
No coma at admission	992/1020 (97)	6/1020 (<1)	22/1020 (2)			
Age group						
≤30 days (94 episodes)				0.002	69/94 (73)	<0.001
Coma at admission	28/43 (65)	0	15/43 (35)			
No coma at admission	37/46 (80)	0	9/46 (20)			
>30 days (1087 episodes)				<0.001	1063/1087 (98)	
Coma at admission	69/77 (90)	0	8/77 (10)			
No coma at admission	955/974 (98)	6/974 (<1)	13/974 (1)			
>30 days to 2 yr (171 episodes)				0.13	168/171 (98)	0.10
Coma at admission	8/8 (100)	0	0			
No coma at admission	155/159 (97)	1/159 (<1)	3/159 (2)			
>2 to 12 yr (479 episodes)				0.005	464/479 (97)	0.18
Coma at admission	22/28 (79)	0	6/28 (21)			
No coma at admission	430/439 (98)	2/439 (<1)	7/439 (2)			
>12 yr (437 episodes)				<0.001	431/437 (99)	<0.001
Coma at admission	39/41 (95)	0	2/41 (5)			
No coma at admission	370/376 (98)	3/376 (<1)	3/376 (< 1)			
Diagnosis						
Carbamyl phosphate synthetase deficiency (203 episodes)				0.11	197/203 (97)	0.44
Coma at admission	10/12 (83)	0	2/12 (17)			
No coma at admission	177/184 (96)	3/184 (2)	4/184 (2)			
Ornithine transcarbamylase deficiency						
Male patients (278 episodes)				0.02	253/278 (91)	<0.001
Coma at admission	23/34 (68)	0	11/34 (32)			
No coma at admission	218/228 (96)	0	10/228 (4)			
Female patients (376 episodes)				0.001	367/376 (98)	0.04
Coma at admission	18/24 (75)	0	6/24 (25)			
No coma at admission	340/344 (99)	1/344 (<1)	3/344 (< 1)			
Argininosuccinate synthetase deficiency (305 episodes)				<0.001	298/305 (98)	0.07
Coma at admission	37/40 (93)	0	3/40 (7)			
No coma at admission	250/256 (98)	2/256 (<1)	4/256 (2)			
Argininosuccinate lyase deficiency (14 episodes)				0.03	13/14 (93)	0.45
Coma at admission	7/7 (100)	0	0			
No coma at admission	5/6 (83)	0	1/6 (17)			

* Three patients with arginase deficiency were treated with sodium phenylacetate and sodium benzoate; one had neonatal onset of the disease and died during the first episode, and two had a total of four episodes and survived. Because ornithine transcarbamylase deficiency is an X-linked disorder, male patients typically have a more severe clinical phenotype than do female patients, so for this disorder a distinction on the basis of sex was made. Patient status at discharge was based on the number of episodes of hyperammonemia for which coma status at both admission and discharge were known (291 patients and 1140 episodes).

† P values were calculated with the use of the McNemar test for the comparison between survival status at discharge (alert plus comatose vs. deceased) and coma status at admission (coma vs. no coma).

‡ P values were calculated with the use of Fisher's exact test for the comparison between survival status in each age subgroup and all other age subgroups and between each subgroup according to diagnosis and all other subgroups according to diagnosis.

Table 3. **Reported Adverse Events in Patients with Urea-Cycle Disorders Treated with Sodium Phenylacetate and Sodium Benzoate.***

Variable	Neonates		Older Patients	
	Patients (N=93)	Episodes of Hyperammonemia (N=94)	Patients (N=239)	Episodes of Hyperammonemia (N=1087)
	number (percent)			
Total no.†	50 (54)	50 (53)	125 (52)	299 (28)
Blood and lymphatic system disorders	11 (12)	11 (12)	20 (8)	21 (2)
Anemia	5 (5)	5 (5)	7 (3)	8 (<1)
Disseminated intravascular coagulation	3 (3)	3 (3)	6 (3)	6 (<1)
Thrombocytopenia	3 (3)	3 (3)	1 (<1)	1 (<1)
Cardiac disorders	9 (10)	9 (10)	17 (7)	23 (2)
Cardiac arrest	3 (3)	3 (3)	2 (<1)	2 (<1)
Tachycardia	2 (2)	2 (2)	8 (3)	13 (1)
Supraventricular tachycardia	2 (2)	2 (2)	0	0
Gastrointestinal disorders	5 (5)	5 (5)	42 (18)	94 (9)
Vomiting	3 (3)	3 (3)	29 (12)	70 (6)
Diarrhea	1 (1)	1 (1)	10 (4)	10 (<1)
General disorders and administration-site conditions	7 (8)	7 (7)	34 (14)	72 (7)
Injection-site reactions	1 (1)	1 (1)	30 (13)	43 (4)
Fever	0	0	16 (7)	25 (2)
Hepatobiliary disorders	3 (3)	3 (3)	5 (2)	5 (<1)
Infections and infestations	7 (8)	7 (7)	33 (14)	44 (4)
Urinary tract infection	0	0	11 (5)	11 (1)
Otitis media	0	0	5 (2)	6 (<1)
Metabolism and nutrition disorders	20 (22)	20 (21)	56 (23)	85 (8)
Hypokalemia	5 (5)	5 (5)	27 (11)	35 (3)
Hyperammonemia	5 (5)	5 (5)	13 (5)	22 (2)
Hyperglycemia	5 (5)	5 (5)	12 (5)	14 (1)
Acidosis	4 (4)	4 (4)	18 (8)	20 (2)
Nervous system disorders	17 (18)	17 (18)	63 (26)	90 (8)
Seizures	8 (9)	8 (9)	25 (10)	29 (3)
Cerebral edema	3 (3)	3 (3)	12 (5)	13 (1)
Mental impairment	1 (1)	1 (1)	22 (9)	27 (2)
Psychiatric disorders	1 (1)	1 (1)	20 (8)	31 (3)
Agitation	0	0	10 (4)	10 (<1)
Renal and urinary disorders	4 (4)	4 (4)	6 (3)	6 (<1)
Respiratory, thoracic, and mediastinal disorders	13 (14)	13 (14)	35 (15)	56 (5)
Respiratory distress or failure	7 (8)	7 (7)	13 (5)	15 (1)
Hyperventilation	1 (1)	1 (1)	5 (2)	8 (<1)
Skin and subcutaneous-tissue disorders	3 (3)	3 (3)	17 (7)	29 (3)
Vascular disorders	12 (13)	12 (13)	12 (5)	12 (1)
Hypotension	12 (13)	12 (13)	4 (2)	4 (<1)

* Reported adverse events are shown according to patient's age, frequency of occurrence event, and frequency of occurrence during episodes of hyperammonemia.
† Some patients had more than one adverse event.

Table 4. **Outcomes of 823 Episodes of Hyperammonemia, According to Age and Peak Ammonium Level.***

Episode	Survival	P Value†
	no. of episodes/total no. (%)	
Peak ammonium level		
≤200 μmol/liter	341/347 (98)	
>200–500 μmol/liter	361/366 (99)	0.77
>500–1000 μmol/liter	56/67 (84)	<0.001
>1000 μmol/liter	20/43 (47)	<0.001
Peak ammonium level at age ≤30 days (74 episodes)		
≤200 μmol/liter	9/10 (90)	
>200–500 μmol/liter	17/18 (94)	1.00
>500–1000 μmol/liter	13/17 (76)	0.18
>1000 μmol/liter	11/29 (38)	<0.001
Peak ammonium level at age >30 days to 2 yr (119 episodes)		
≤200 μmol/liter	49/50 (98)	
>200–500 μmol/liter	55/55 (100)	0.48
>500–1000 μmol/liter	5/6 (83)	0.11
>1000 μmol/liter	7/8 (88)	0.19
Peak ammonium level at age >2 yr to 12 yr (305 episodes)		
≤200 μmol/liter	140/143 (98)	
>200–500 μmol/liter	129/132 (98)	1.00
>500–1000 μmol/liter	23/28 (82)	0.001
>1000 μmol/liter	0/2	0.002
Peak ammonium level at age >12 yr (325 episodes)		
≤200 μmol/liter	143/144 (99)	
>200–500 μmol/liter	160/161 (99)	1.00
>500–1000 μmol/liter	15/16 (94)	0.14
>1000 μmol/liter	2/4 (50)	0.001

* Survival according to peak ammonium level was based on the number of episodes for which ammonium data were available. To convert values for ammonium to micrograms per deciliter, divide by 0.5543.

† P values were calculated by Fisher's exact test for the comparison between survival status for subgroups according to peak ammonium level and subgroups according to all lower peak ammonium levels (≤200 μmol/liter for the comparison with >200 to 500 μmol/liter; ≤200 μmol/liter and >200 to 500 μmol/liter for the comparison with >500 to 1000 μmol/liter).

with urea-cycle disorders who were in hyperammonemic coma resulted in a prompt decrease in the plasma ammonium level and clinical improvement.[14] In an additional study involving 26 patients with urea-cycle disorders who had hyperammonemia, prolonged survival and improved clinical outcome were observed after treatment with intravenous sodium benzoate and arginine hydrochloride, dietary restriction of protein, provision of adequate calories, and peritoneal dialysis.[15] Subsequently, a study involving seven children with urea-cycle disorders showed that a combination of intravenous sodium phenylacetate, sodium benzoate, and arginine hydrochloride, with non-nitrogenous intravenous hyperalimentation, could lower plasma ammonium to normal or near-normal levels.[16]

The 299 patients with urea-cycle disorders in the present observational study sustained 1181 episodes of hyperammonemia over a 25-year period, with a survival rate of 96% (neonates, 73%; patients more than 30 days old, 98%) and a rate of overall survival of 84%. The use of alternative-pathway therapy in addition to provision of appropriate nutrition and, in some cases, the use of dialysis, clearly improved survival, as compared with historical data. Because the patients were treated

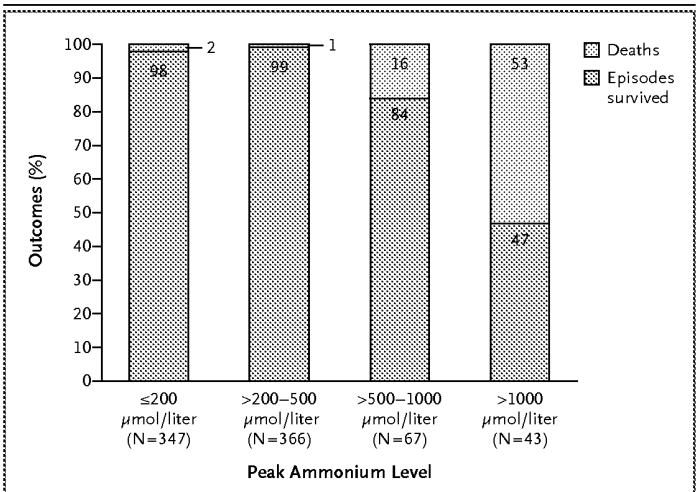

Figure 2. Episodes Survived According to Peak Ammonium Levels.
The percentage of episodes of hyperammonemia survived according to peak ammonium levels was based on the number of episodes for which data on plasma ammonium levels were available.

primarily at metabolic centers with experience in caring for acute hyperammonemia caused by urea-cycle disorders, the high rate of survival probably reflects, in part, the expertise available at the treating institutions. In addition, these survival statistics apply only to patients who received the study drug and may not apply to all patients with urea-cycle disorders. Some patients may not have been treated because their condition was poor on presentation, and others may have died without hospitalization. Despite these possibilities, the survival rate in our cohort is remarkable and confirms the promise of initial reports showing improved survival after alternative-pathway therapy in a relatively small number of patients with urea-cycle disorders.[9,15,16] This point is further highlighted when data for the current cohort are compared with recently reported outcome data for 217 patients with urea-cycle disorders who did not receive alternative-pathway therapy for acute management of hyperammonemia.[17] Of those patients, only 16% with neonatal onset of the disease survived overall, and survival among those with late onset of disease was 72%.[17]

Not surprisingly, patients were more likely to survive if they were not comatose at the time of admission. However, the majority (81%) of patients who were comatose at admission survived. Survival was also related to the peak plasma ammonium level and to age. Nearly all episodes in which the ammonium level did not exceed 500 μmol per liter (902 μg per deciliter) resulted in survival, with survival decreasing with rising ammonium levels. A substantial decrease in plasma ammonium levels was noted in survivors, but not in those who died after a hyperammonemic crisis. This finding may reflect the presence of a severe accumulation of waste nitrogen that was refractory to treatment. It is also possible that treatment was withdrawn in some cases because of poor clinical status and prognosis, leading to persistently high ammonium levels.

Adverse events were reported in just over 50% of treated patients (Table 3). However, most adverse events were likely to be related to the underlying primary disease or the patient's clinical status. Among those who died, seizures, infection, and cerebral edema were the most common coexisting conditions. Cerebral edema or increased intracranial pressure was documented by investigators in 16 of 49 deaths but, given the reported elevated levels of ammonium, was likely to have been present in nearly all cases. An overdose of sodium phenylacetate and sodium benzoate was also reported relatively frequently in patients who died and was noted in 13 cases. Massive overdose was uncommon, with two instances of doses between 9 and 17 times the recommended dose of sodium phenylacetate and sodium benzoate documented. It is likely that many of the cases of mild overdosing (e.g., one or two additional bolus infusions given over several days) are a reflection of the severity of the episode of hyperammonemia and the poor clinical status of patients who eventually died. Continuous high rates of intravenous infusion may result in plasma phenylacetate levels that saturate the capacity for conversion of phenylacetate to phenylacetylglutamine, leading to rapid accumulation of phenylacetate and subsequent toxicity.[18,19] Clearly written medical prescriptions and cross-checking of drug doses are important safeguards. Furthermore, because the *N*-acyltransferases that conjugate glutamine and glycine to phenylacetate and benzoate, respectively, are located in the liver and kidney, patients with liver or kidney failure or both may not be candidates for these medications.

Various neurologic outcomes among patients treated with sodium phenylacetate and sodium benzoate have been documented.[15,20] Of 23 survivors of neonatal hyperammonemic coma treated with sodium phenylacetate and sodium benzoate,

10 had normal development, 7 had mild mental retardation, and 6 had moderate-to-severe mental retardation.[15] Another study documented mental impairment in the majority of children (26) surviving neonatal episodes of hyperammonemic coma, with 79% having one or more developmental disabilities at 12 to 74 months of age.[20] Nevertheless, normal intelligence is clearly possible after a hyperammonemic event and appears to depend on the duration of coma and the extent of brain damage.[15,20-22] The establishment of a network of specialized centers with expertise in providing state-of-the-art treatment for metabolic disorders offers the potential for improving neurologic outcomes.[23] To this end, the National Institutes of Health sponsored the formation of a Rare Disease Clinical Research Center Network for urea-cycle disorders. The prospective treatment of neonates at risk for hyperammonemia and the use of liver transplantation in patients with urea-cycle disorders both play a significant role in the treatment of such patients and may improve outcome.[24-27] Hepatocyte transplantation has been attempted in a few patients with urea-cycle disorders and holds promise for the future.[28]

Alternative-pathway therapy was effective in lowering plasma ammonium levels in most patients. However, dialysis was frequently used in neonates (60%) and used relatively rarely in older patients (7%), findings that reflect common clinical practice. One accepted type of therapy for neonates with hyperammonemic coma and ammonium levels greater than 300 μmol per liter (541 μg per deciliter) is to initiate hemodialysis concomitantly with sodium phenylacetate, sodium benzoate, and arginine therapy. Conventional hemodialysis has the highest ammonium clearance rate, as compared with other methods such as peritoneal dialysis, exchange transfusion, and hemofiltration.[24,29] In older patients, alternative-pathway therapy is the mainstay, and dialysis is used only when ammonium levels do not decline after maximal treatment or when obtundation or coma persist. We think that timely administration of alternative-pathway therapy may reduce or eliminate the need for hemodialysis, depending on the level and duration of the hyperammonemia, the stage of coma, and the presence or absence of brain edema, but prospective, multicenter trials involving patients of all ages are needed to address the role of hemodialysis further.

Although survival among patients with urea-cycle disorders has clearly been improved after treatment of episodes of hyperammonemia with sodium phenylacetate and sodium benzoate and other supportive care, overall neurologic outcomes remain to be evaluated in detail. Studies documenting long-term follow-up and careful developmental testing are needed.

Supported in part by grants from the General Clinical Research Centers (GCRC) at Johns Hopkins University (M01-RR-00052), Children's Hospital of Philadelphia (M01-RR-000240), and Children's National Medical Center (M01-RR-020359); grants to Dr. Brusilow (U.S. Public Health Service, National Institute of Child Health and Human Development, 11134 and 26358, and the Food and Drug Administration, FD-R000198); and the National Center for Research Resources during early phases of this study, through support of the national GCRC network.

Dr. Enns reports receiving a lecture fee from Ucyclyd Pharma; Drs. Enns, S.A. Berry, G.T. Berry, Rhead, and Hamosh, consulting fees for service at a single meeting of the advisory board of Ucyclyd Pharma; and Dr. Brusilow, consulting fees from Ucyclyd Pharma. No other potential conflict of interest relevant to this article was reported.

We thank Ucyclyd Pharma for providing access to its database for urea-cycle patients; E. Glynn and J. Mauney, Kendle International, for assistance with the statistical analysis and data review; M. Batshaw for his tireless commitment to patients with urea-cycle disease and their treatment; and the patients, their families, and the clinicians who have cared for them.

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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

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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

	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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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

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

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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.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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

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

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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 5362f6c61e8309894e286bcc6da28b2583c1d937	no	11
Warnings:					
Information:					

2	Non Patent Literature	ISR_WO.pdf	398953 5763d426b44557fd539b95e2fa5b181f10f49e19	no	8
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3	Information Disclosure Statement (IDS) Form (SB08)	Supplemental_IDS_8003US02.pdf	612460 ed1fc1852741f6b2c315e54071b1396fcccb9f9f	no	4
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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.

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

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

79532-8003.WO00
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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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

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

PCT

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

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 20 JUN 2012
Applicant's or agent's file reference 795328003WO	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.

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.	

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	1	20100008859	A1	2010-01-14	SCHARSCHMIDT	

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/Savitha Rao/ 11/15/2012

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Receipt date: 06/28/2012	Application Number	13417137 13417137 - GAU: 1629
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	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.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Savitha Rao/	Date Considered	11/15/2012

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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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

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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.	
	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.	

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				First Named Inventor	Bruce SCHARSCHMIDT
				Group Art Unit	1629
				Examiner Name	To be assigned
Sheet	2	of	10	Attorney Docket No.	79532.8003.US02

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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.	
	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.	

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				Group Art Unit	1629
				Examiner Name	To be assigned
Sheet	3	of	10	Attorney Docket No.	79532.8003.US02

OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS			
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	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.	
	C20	CHANG J.-G., et al., "Treatment of Spinal Muscular Atrophy by Sodium Butyrate," PNAS USA (2001) 98(17):9808-9813.	
	C21	ClinicalTrials.Gov/Archive View of NCT00551200 on 2007_12_11 "Dose-Escalation Safety Study of Glyceryl Tri (4-Phenylbutyrate)(GT4P) to Treat Urea Cycle Disorders" [accessed 5 October 2009], 4 pages.	
	C22	Combined Search and Examination Report mailed on September 9, 2010, for Great Britain Patent Application No. 1013468.2, filed on August 27, 2009, six pages.	

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				Group Art Unit	1629
				Examiner Name	To be assigned
Sheet	4	of	10	Attorney Docket No.	79532.8003.US02

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				Confirmation Number	6423
				Filing Date	2012-03-09
				First Named Inventor	Bruce SCHARSCHMIDT
				Group Art Unit	1629
				Examiner Name	To be assigned
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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.
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


=> FIL STNGUIDE
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      11.77      13.45

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LAST RELOADED: Nov  9, 2012 (20121109/UP).

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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

=> file caplus
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   1.62      15.07

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

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
        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.
OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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

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

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

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

=> d l11 1-9 ibib ab

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

0.109 for PAA. In summary, the LC-ESI-MS method developed in this study is simple, sensitive and reliable.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1275522 CAPLUS
DOCUMENT NUMBER: 156:626560
TITLE: Macromolecular prodrugs based on synthetic polyaminoacids: drug delivery and drug targeting in antitumor therapy
AUTHOR(S): Cavallaro, Gennara; Pitarresi, Giovanna; Giammona, Gaetano
CORPORATE SOURCE: Dipartimento di Chimica e Tecnologie Farmaceutiche, Universita degli Studi di Palermo, Palermo, 90123, Italy
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) (2011), 11(18), 2382-2389
CODEN: 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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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

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
C:\Users\srao3\Documents\EAST\Workspaces\13417137.wsp

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BIB DATA SHEET

CONFIRMATION NO. 6423

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
03/22/2012

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

FILING FEE RECEIVED		
1030	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

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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

34055 7590 11/21/2012

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SEATTLE, WA 98111-1208

EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
11/21/2012	ELECTRONIC

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

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

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

patentprocurement@perkinscoie.com

Office Action Summary	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 --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *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

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:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		OAResponse.pdf	119786 cc67f3b37c264024b014ae9c8dad95b84cb93e9a	yes	10

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	10
Warnings:			
Information:			
	Total Files Size (in bytes):	119786	

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.

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.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/417,137	03/09/2012	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ 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 ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
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".

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

Legal Instrument Examiner:
/DORIS BURNS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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
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S9	8	S7 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S10	2	S9 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/11/15 14:08
S11	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR; 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			
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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

			DERWENT			
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
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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
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S62	0	S55 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S63	8	S61 and nitrogen	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S64	2	S63 and scavenging	US-PGPUB; USPAT; USOCR; DERWENT	OR	OFF	2012/12/20 16:43
S65	109	"nitrogen scavenging"	US-PGPUB; USPAT; USOCR;	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

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                  Exposure Toxicity Data
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                  Organization Becomes 63rd Authority on CA/CAplus
 NEWS 13  APR 16  DWPI Database (WPINDEX, WPIDS, WPIX) Enhanced with
                  Numerical Property Search Feature
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                  Profiles and Saved Answers
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                  CSA Databases Allows More Efficient Searching on STN
 NEWS 27  JUL 30  Reload of ENCOMPPAT/2 Databases
 NEWS 28  JUL 30  More Experimental Property Data in CAS REGISTRY
 NEWS 29  AUG  1  Reload of ReaxysFile on STN - Significantly More Content Added
                  and Updates are Resumed
 NEWS 30  AUG  1  Redesigned CAS Website to be Launched on August 5, 2012
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 NEWS 31  AUG  6  INPADOC: German Patent Coverage Resumed
 NEWS 32  SEP 10  Get More Current Reaction Information with Daily Updates to
                  CASREACT
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                  Biomedical and Pharmacological Content from Conferences
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                  and Saved Answers

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

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=> 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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     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

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             0 "SCAVENGING"
             0 "NITROGEN SCAVENGING"
                 ("NITROGEN"(W)"SCAVENGING")
             0 BUTYRIC
L3           0 L1 AND BUTYRIC

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

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

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REVISED CLASS FIELDS (/NCL) LAST RELOADED:  September 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.

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

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

=> d l11 1-9 ibib ab

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

L11  ANSWER 2 OF 9  CAPLUS  COPYRIGHT 2012 ACS on STN
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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

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


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

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

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

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

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USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  November 2012

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

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

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

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

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

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

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

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

L2 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN

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

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

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

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

L2 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:397345 CAPLUS

DOCUMENT NUMBER: 155:453598

TITLE: Lysinuric protein intolerance: reviewing concepts on a multisystem disease

AUTHOR(S): Sebastio, Gianfranco; Sperandeo, Maria P.; Andria, Generoso

CORPORATE SOURCE: Department of Clinical Pediatrics, Federico II University of Naples, Italy

SOURCE: American Journal of Medical Genetics, Part C: Seminars in Medical Genetics (2011), 157(1), 54-62
CODEN: AJMGFC; ISSN: 1552-4868

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

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

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

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

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

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

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

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

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

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

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

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

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

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

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

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

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

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

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L2            11 S L1 AND AMMONIA

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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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

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

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.

PTOL-85 (Rev. 02/11)

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

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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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UNITED STATES DEPARTMENT OF COMMERCE
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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.

PTOL-85 (Rev. 02/11)

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

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		INTERNATIONAL CLASSIFICATION									
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED				
424	9.2	A	6	1	K	49 / 00 (2006.0)					
CROSS REFERENCE(S)		A	6	1	P	13 / 00 (2006.01.01)					

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

☐ 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:**	
		11	
(Assistant Examiner)	(Date)		
/SAVITHA RAO/ Primary Examiner.Art Unit 1629	12/20/2012	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1

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**

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_79532800 2US2.pdf	122178 b143c577d206dc04c813d4eeb4beb10500d16815	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31933 ccbaf6817a2240ce35d16163b80cc38c069faf45	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.

PART B - FEE(S) TRANSMITTAL

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

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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 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).

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 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.

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	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)

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

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

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

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

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

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 c21efe6754b43f7d4aa0c4894099e8dec7d4357b	no	1
Warnings:					
Information:					

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

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/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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(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
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

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**

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

■ Practitioners associated with Customer Number: 101325

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to.

■ The address associated with Customer Number: 101325

OR

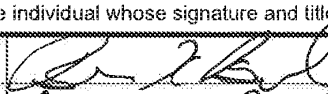
☐	Firm or Individual Name		
	Address		
	City	State	Zip
	Country		
	Telephone	Email	

Assignee Name and Address: Horizon Therapeutics, Inc.
533 Bryant, Suite #6
Palo Alto, CA 94301

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	5/1/15
Name	Brian K. Beeler	Telephone	847-502-5250
Title	Senior VP, Legal		

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

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office;U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of1995, no persons arerequired to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: HORIZON THERAPEUTICS, INC.

Application No./Patent No.: As set forth on the attached Schedule A Filed/Issue Date: As set forth on the attached Schedule A

Titled: _____

HORIZON THERAPEUTICS, INC., a Delaware Corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel See Schedule A, Frame See Schedule A, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Dennis A. Bennett/	May 15, 2015
Signature	Date
Dennis A. Bennett	Attorney of Record, Reg No. 34547
Printed or Typed Name	Title or Registration Number

Schedule A

Docket No.	Application No.	Application Date	Reel/Frame No.	Recordation Date
079532-8001.US01	12/350,111	2009-01-07	022305 / 0387 025031 / 0014 028014 / 0894 035638 / 0305	02/24/2009 09/22/2010 04/09/2012 05/14/2015
079532-8003.US02	13/417,137	2012-03-09	028014 / 0894 035638 / 0305	04/09/2012 05/14/2015
079532-8003.US03	13/775,000	2013-02-22	035361 / 0777 035638 / 0305	04/08/2015 05/14/2015
079532-8004.US01	13/610,580	2012-09-11	029337 / 0054 035638 / 0305	11/21/2012 05/14/2015
079532-8005.US02	14/086,870	2013-11-21	035361 / 0777 035638 / 0305	04/08/2015 05/14/2015
079532-8007.US00	61/890,827	2013-10-14	035361 / 0777 035638 / 0305	04/08/2015 05/14/2015
079532-8007.US01	62/044,168	2014-08-29	035361 / 0777 035638 / 0305	04/08/2015 05/14/2015
079532-8007.US02	14/514,334	2014-10-14	035361 / 0777 035638 / 0305	04/08/2015 05/14/2015

Electronic Acknowledgement Receipt

EFS ID:	22363871
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:	Dennis A. Bennett/Ronnie Almira
Filer Authorized By:	Dennis A. Bennett
Attorney Docket Number:	79532.8003.US02
Receipt Date:	15-MAY-2015
Filing Date:	09-MAR-2012
Time Stamp:	16:59:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	HorizonTherapeutics-POA_Assignee.pdf	96506 cb08b2aa2de030cfca8e0ff6ce3b34f18d522e9f	no	1

Warnings:

Information:

2	Assignee showing of ownership per 37 CFR 3.73	HOR_373-Statment_Schedule_A.pdf	157428 6c05c96d65f079637c44f6e854cbea479726c476	no	3
Warnings:					
Information:					
			Total Files Size (in bytes):	253934	

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

POWER OF ATTORNEY NOTICE

OC000000075366654

Date Mailed: 05/27/2015

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/15/2015.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

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

/agizaw/

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	079532.8003.US02

CONFIRMATION NO. 6423

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

POA ACCEPTANCE LETTER

OC000000075366691

Date Mailed: 05/27/2015

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/15/2015.

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

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

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Paper No. 13
Filed: November 4, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.,
Petitioner,

v.

HORIZON THERAPEUTICS, INC.[1],
Patent Owner.

Case IPR2015-01127
Patent 8,404,215 B1

Before TONI R. SCHEINER, DEBORAH KATZ, and GRACE KARAFFA OBERMANN, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

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[1] "[E]ffective May 7, 2015, the name of Hyperion Therapeutics, Inc., was changed to Horizon Therapeutics, Inc. . . . Accordingly, Horizon Therapeutics, Inc. . . . is the Patent Owner of U.S. Patent No. 8,642,012." (Paper 5, 2.)

I. BACKGROUND

Par Pharmaceutical, Inc. ("Petitioner") filed a request for an *inter partes* review ("IPR") of claims 1–11 of U.S. Patent No. 8,404,215 B1 (Ex. 1001 ("the '215 patent")) (Paper 2 ("Pet.")) and was accorded a filing date of April 29, 2015 (Paper 3). Hyperion Therapeutics, Inc. ("Patent Owner") timely filed a Preliminary Response (Paper 8 ("Prelim. Resp.")).

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless Petitioner shows that there is "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Petitioner makes that showing with respect to some of the grounds for unpatentability of claims 1–11. Therefore, we institute review as to claims 1–11.

Our findings of fact and conclusions of law are based on the record developed thus far, prior to Patent Owner's Response. This is not a final decision as to the patentability of any challenged claim. If a final decision is issued in this case, it will be based on the full record developed during trial.

A. Related proceedings

Petitioner and Patent Owner identify *Hyperion Therapeutics Inc. v. Par Pharmaceutical, Inc.*, Case No. 14-cv-00384 (E.D. Tex.), filed April 23, 2014 in the U.S. District Court for the Eastern District of Texas by Patent Owner, as a related matter. (Pet. 6.; Patent Owner's Initial Mandatory Notices filed June 17, 2015 at 3.) Petitioner indicates that Patent Owner served the complaint on April 29, 2014, alleging that Petitioner has infringed two of its patents, including the '215 patent.

Petitioner indicates that it has also filed a second petition for an *inter partes* review of Hyperion's U.S. Patent 8,642,012 B1, but represents that the '215 patent is not related to that patent. (Pet. 7.)

B. The '215 patent (Ex. 1001)

The '215 patent is entitled "**METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING**." (Ex. 1001.) It issued from an application filed March 9, 2012, and claims priority to two provisional applications filed November 29, 2011 and September 30, 2011. (Ex. 1001 coversheet.) Petitioner's witness, Neal Sondheimer, M.D., Ph.D.[2], testifies that nitrogen scavenging is a therapy using drugs to treat nitrogen retention disorders. (Ex. 1002 ¶ 17.) These disorders occur, for example, in urea cycle disorders ("UCDs"), wherein the body is unable to remove excess nitrogen waste. (*Id.* ¶ 18.) When the body functions normally, dietary amino acids are converted first to ammonia and then to urea in the urea cycle and, finally, excreted in the urine. (*Id.*) In UCDs, the enzymes controlling this urea cycle are deficient, leading to dangerously high levels of ammonia in the blood, causing lethargy, coma, brain damage, or even death. (*Id.*)

[2] Petitioner relies on the testimony of Neal Sondheimer, M.D., Ph.D. (Ex. 1002). Dr. Sondheimer testifies that he currently holds several positions at the Children's Hospital of Philadelphia and the University of Pennsylvania, including Attending Physician in the Division of Biochemical Genetics, Training Director for the Clinical Biochemical Genetics Group, Program Director for Medical Genetics, and Assistant Professor of Pediatrics. (Ex. 1002 ¶ 10.) Dr. Sondheimer testifies that he has been involved in several research studies about the treatment of urea cycle defects and has co-authored several publications about the use of ammonia-scavenging medications. (*Id.* ¶ 12.) At this stage of the proceeding, we find Dr. Sondheimer to be qualified to provide opinions on the subject matter at issue.

Nitrogen scavenging drugs treat UCDs by providing an alternative pathway to remove excess ammonia. (*Id.* ¶ 21.) These drugs, including sodium benzoate and phenylacetic acid, remove ammonia ions from the blood and allow them to be excreted. (*Id.*) Dr. Sondheimer testifies that these drugs were known before the priority date claimed for the '215 patent. (*Id.*, citing Ex. 1012, 147–48 and Ex. 1015, 10–11 and 13.)

The '215 patent has three independent claims: claims 1, 2, and 3. For the purposes of our analysis, claim 1 of the '215 patent is illustrative. Claim 1 recites:

> **1**. A method for adjusting the dosage of a nitrogen scavenging drug in a subject who has previously been administered an initial dosage of the 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 dosage *if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.*

(Ex. 1001, 24:28–39 (emphasis added).)

Each of Patent Owner's independent claims is drawn to a method of adjusting the dosage of a nitrogen scavenging drug, wherein the fasting blood ammonia level of the subject is measured and compared to the "upper limit of normal for blood ammonia." (Ex. 1001, 24:28–57.) This comparison is used to determine whether "the fasting blood ammonia level

is greater than half the upper limit of normal for blood ammonia level," and if so, the nitrogen scavenging drug is administered.[3] (*Id.*)

Independent claims 2 and 3 also include a limitation to administering the nitrogen scavenging drug when a subject's fasting blood ammonia level is greater than half the upper limit of normal.

C. Applied Prior Art

Petitioner relies on the following prior art references:

Abbreviation	Citation	Exhibit Number
Fernandes	INBORN METABOLIC DISEASES: DIAGNOSIS AND TREATMENT, 214–22 (J. Fernandes et al. eds., 3d ed. 2000).	1011
Blau	PHYSICIAN'S GUIDE TO THE LABORATORY DIAGNOSIS OF METABOLIC DISEASES, 261–76 (Nenad Blau et al. eds., 2d ed. 1996).	1006
Simell	Olli Simell et al., *Waste Nitrogen Excretion Via Amino Acid Acylation: Benzoate and Phenylacetate in Lysinuric Protein Intolerance*, 20 PEDIATRIC RESEARCH 1117–21 (1986).	1005
'859 Publication	U.S. Patent Publication No. 2010/0008859 A1, filed January 7, 2009, published January 14, 2010.	1008
Brusilow '91	Saul W. Brusilow, *Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion*, 29 PEDIATRIC RESEARCH 147–150 (1991).	1012

[3] In claims 1 and 3, the dosage of nitrogen scavenging drug administered is greater than an *initial* dose originally administered to the subject. In claim 2, an initial dose of nitrogen scavenging drug is not specified. (Ex. 1001, 24:28–57.)

Brusilow '84	Saul W. Brusilow et al., *Treatment of Episodic Hyperammonia in Children with Inborn Errors of Urea Synthesis*, 310 THE NEW ENGLAND JOURNAL OF MEDICINE 1630–34 (1984).	1004
Dixon	Majorie A. Dixon et al., *Intercurrent illness in inborn errors of intermediary metabolism*, 67 ARCHIVES OF DISEASE IN CHILDHOOD 1387–91 (1992).	1010
Scientific Discussion	*Scientific Discussions*, EMEA, 1–12 (2005) (discussion for Ammonpas) (reportedly available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000219/WC500024748.pdf)	1009

D. Asserted Grounds of Unpatentability

Petitioner challenges the patentability of '215 patent claims 1–11 under 35 U.S.C. § 103 over the following groups of references:

Ground	References	Claims
1	Fernandes in view of Blau, Simell, and the '859 Publication	1, 3–7, and 9
2	Fernandes in view of Blau, Simell, and Brusilow '91	8
3	Fernandes in view of Blau, Simell, and the '859 Publication	10–11
4	Fernandes and Brusilow '84 in view of Blau, and Simell	2, 4–7, 9, and 10
5	Fernandes and Brusilow '84 in view of Blau, Simell, and Brusilow '91	8
6	Fernandes and Brusilow '84 in view of Blau, Simell, and the '859 Publication	11
7	Scientific Discussion in view of Blau and Dixon	1–7 and 9
8	Scientific Discussion in view of Blau, Dixon, and Brusilow '91	8

9	Scientific Discussion in view of Blau, Dixon, and the '859 Publication	10–11

II. Analysis

Under 35 U.S.C. § 103 subject matter is unpatentable "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007), the Supreme Court explained that if the person of ordinary skill could have arrived at the claimed subject matter using common sense to combine different teachings of the prior art, that subject matter is likely obvious, not innovative.

A. Ground 1

Petitioner cites to Fernandes, Blau, Simell, and the '859 Publication to argue that Patent Owner's claims 1, 3–7, and 9 would have been obvious. (Pet. 12–23.) As Petitioner notes, Fernandes teaches treating UCDs with nitrogen scavenging drugs, including sodium benzoate (which is recited in dependent claim 7) and phenylbutyrate. (Pet. 13, citing Ex. 1011, 219.) Fernandes also teaches that plasma ammonia levels should be regularly monitored to determine dosing of these drugs, with the goal of keeping the level of ammonia in the blood below 80 μmol/L. (Ex. 1011, 219 ("All treatment must be monitored with regular quantitative estimation of plasma ammonia and amino acids, paying particular attention to the concentrations of glutamine and essential amino acids. The aim is to keep plasma ammonia levels below 80 μmol/l . . .").)

Petitioner relies on Figure 17.2 on page 220 of Fernandes, which is reproduced below, to show that Fernandes teaches adjusting the dosage of nitrogen scavenging drugs in response to the level of ammonia in the blood.

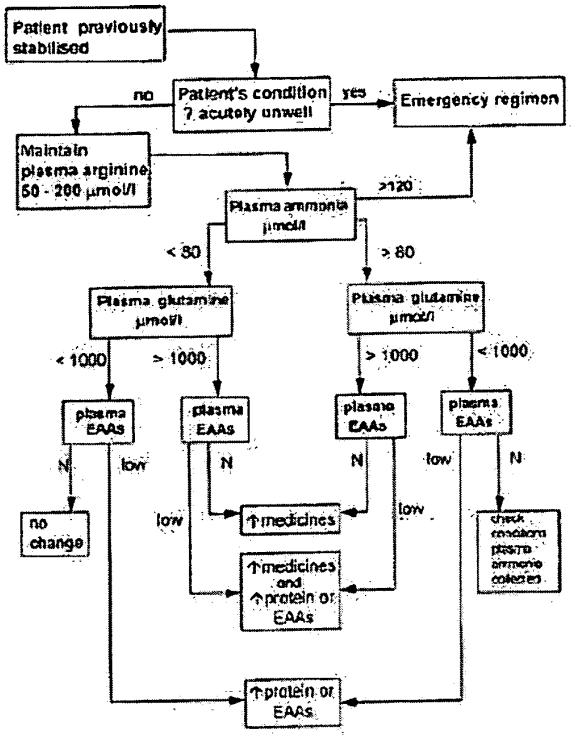

Figure 17.2, reproduced above, depicts a flow chart for management of patients with UCDs, wherein the plasma ammonia level of a patient who was previously stabilized is evaluated. Following the flow chart of Figure 17.2, if the plasma ammonia level is either greater than or less than 80 µmol/L, the levels of glutamine and essential amino acids in the plasma are evaluated. Depending on the levels of these substances, Figure 17.2 indicates whether medicines should be increased. Petitioner argues that Figure 17.2 shows that Fernandes teaches increasing the dose of a nitrogen scavenging drug when the measured plasma ammonia is greater than 80 µmol/L. (*See* Pet. 13.)

Petitioner argues further that Fernandes teaches increasing the dosage of the nitrogen scavenging drug sodium benzoate from 250 mg/kg/day to 500 mg/kg/day. (Pet. 20, citing Ex. 1011, 219 ("Sodium benzoate is usually

given in doses up to 250 mg/kg/day but, in acute emergencies, this can be increased to 500 mg/kg/day.").)

Petitioner relies on Simell for its teaching that fasting blood ammonia levels were measured in a study of the effects of benzoate and phenylacetate. (Pet. 13–14, citing Ex. 1005, 1117–18.) Similarly, Blau teaches measuring blood ammonia levels at least four hours after the last meal or intravenous amino acid supply when evaluating UCDs. (Pet. 14, citing Ex. 1006, 273.)

Petitioner relies on the '859 Publication for its teaching of a method of adjusting the dose of a nitrogen scavenging drug according to a comparison of the subject's blood ammonia levels with the upper limit of normal for blood ammonia levels. (Pet. 14, citing Ex. 1008 ¶ 94: "As used herein, plasma levels of ammonia are acceptable when they are at or below a level considered normal for the subject, and commonly this would mean plasma ammonia level is below about 40 μmol/L. In certain clinical tests described herein the upper limit of normal for the subjects was between 26 and 35 μmol/L . . . ."; *see also* ¶¶ 63 and 201 and Fig. 3.)

According to Dr. Sondheimer, those of skill in the art would have been motivated to combine the teachings of Fernandes, Simell, Blau, and the '859 Publication, which demonstrate the level of skill in the art at the time, because they relate to different aspects of using nitrogen scavenging drugs for treating UCDs. (Ex. 1002 ¶¶ 44–47 and 49; *see* Pet. 15–16.) Dr. Sondheimer also testifies that in light of these teachings, those of skill in the art would have administered a dose of a nitrogen scavenging drug greater than the initial dose if the measured fasting blood ammonia level is greater than the upper limit of normal. (Ex. 1002 ¶ 57; *see* Pet. 21–22.)

Patent Owner responds to Petitioner's challenge in Ground 1 by arguing that Petitioner has failed to show that any of the cited references teach adjusting the dose of a nitrogen scavenging drug "if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level." (Prelim. Resp. 19.) Patent Owner argues that the critical aspect of their invention is adjustment of drug dosing well *before* the upper limit of normal. (Prelim. Resp. 23.) According to Patent Owner, the art cited by Petitioner does not reflect a "line" for dose adjustment drawn at half the upper limit of normal, but instead teaches a "line" at much higher blood ammonia levels. (*Id.* at 19–24.)

Patent Owner admits that the '215 patent claims do not expressly specify an upper limit of fasting blood ammonia levels, but argues that because ammonia is so toxic to nerve cells an upper limit is set "by the realities of the disorders being treated." (Prelim. Resp. 24.) To support this argument, Patent Owner cites to the '215 patent specification, which defines the "upper limit of normal" as "the highest level in the range of normal values." (Prelim. Resp. 13–14, citing Ex. 1001, 12:18–19; also citing Ex. 1001, 4:39–42, 3:21–22, 47–48, 4:10–11, and 12:47–56.)[4]

Despite Patent Owner's argument, we are persuaded that Petitioner is reasonably likely to prevail. The information presented at this stage of the proceeding does not establish that Patent Owner's claims are limited to

[4] Patent Owner argues that the Petitioner failed to provide a proper claim construction and that, therefore, the Petition should be denied. (Prelim. Resp. 5–11.) We are not persuaded that, if there is any deficiency in the Petition, it is fatal to Petitioner's arguments. Instead, for the purposes of this decision, we are able to understand both Petitioner's and Patent Owner's arguments regarding interpretation of the scope of the challenged claims in a manner sufficient to apply the claims to the asserted prior art.

administering an adjusted dosage based on a measurement of plasma ammonia falling within the range between "greater than half the upper limit of normal" and some upper, unspecified, limit. On this record, under the broadest reasonable interpretation, Patent Owner's claims specify only a lower limit for drug adjustment ("half the upper limit of normal"), not an upper limit. *See* 37 C.F.R. § 42.100(b); *see In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1275–79 (Fed. Cir. 2015). Petitioner shows sufficiently that the claims do not exclude methods where the dose is adjusted when blood ammonia levels are more than half the upper limit of normal.

Patent Owner argues further that Fernandes does not teach adjusting nitrogen scavenging drug dosage when blood ammonia levels are greater than 80 μmol/L because Fernandes bases the adjustment on plasma glutamine levels. (Prelim. Resp. 19–22.) Citing Figure 17.2, Patent Owner argues that under the scheme depicted, medicine is increased when plasma glutamine levels are greater than 1000 μmol/L, regardless of whether the plasma ammonia level is greater or less than 80 μmol/L. (Prelim. Resp. 20.)

We are not persuaded to deny review, however, based on Patent Owner's argument that Fernandes teaches other routes (not covered by the challenged claims) for adjusting the dose of nitrogen scavenging drugs, including a route based on evaluation of glutamine levels. That argument does not detract from Petitioner's showing that Fernandes teaches that at least one path to increasing medicines is when plasma ammonia levels are greater than half the upper limit of normal. At this point in the proceeding, Patent Owner has not directed us to evidence that those of skill in the art would not have appreciated this teaching. Any final decision will be based on the full trial record.

Patent Owner argues further that Fernandes does not teach measuring fasting blood ammonia levels (Prelim. Resp. 19) and that neither Blau, nor Simell, nor the '859 Publication teaches adjusting the dosage of a nitrogen scavenging drug when blood ammonia levels are half the upper limit of normal (Prelim. Resp. 25–27). These references were not cited for the limitation that Patent Owner argues, but others were. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (citing *In re Keller,* 642 F.2d 413, 425 (CCPA 1981)).

Patent Owner argues further that Blau teaches away from using plasma ammonia levels to determine dose adjustment, recommending a "more holistic approach" instead. (Prelim. Resp. 27.) At this stage of the proceeding, the record does not make clear what this "more holistic approach" is. Patent Owner has not directed us to an express description of a "more holistic approach" and has not had the opportunity to present the testimony from the perspective of one skilled in the art about whether the teachings of Blau would discourage those of skill in the art from using a method that includes the steps of the '215 claims to adjust nitrogen scavenging drug dosage. *See* 37 C.F.R. § 42.107(c) (no new testimonial evidence may be submitted with a preliminary response). Accordingly, at this preliminary stage of the proceeding, we are not persuaded us that Blau teaches away from the claimed invention, or otherwise indicates there is not a reasonable likelihood Petitioner will prevail.

In light of the evidence and arguments presented so far, we consider there to be a reasonable likelihood that Petitioner will prevail on the

challenges made in Ground 1. Accordingly, we institute review of claims 1, 3–7, and 9. In making this determination, we do not make a final determination of the patentability of the '215 claims.

B. Grounds 2–4

In Grounds 2–4, Petitioner challenges claims 2, and 4-11. (Pet. 23–38.) We are persuaded, based on the information presented at this stage of the proceeding, that Petitioner is reasonably likely to prevail at trial on Grounds 2–4. We focus our analysis on claims 2, 8, 10, and 11, which are not included in the grounds instituted above.

Briefly, Petitioner's Ground 2 challenges claim 8 of the '215 patent, which recites:

> **8**. 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.

(Ex. 1001, 25:3–5.) In Ground 2, Petitioner cites to Brusilow '91 for its teaching of treatments with the nitrogen scavenging drugs phenylacetate or phenylbutyrate to bring daily plasma ammonia levels to 25.5 $\pm$ 3.3 μmol/L, wherein the upper limit of normal is less than 30 μmol/L. (Pet. 23–24, citing Ex. 1012, 149.) Petitioner relies on the testimony of Dr. Sondheimer to support its argument that those of skill in the art would have been motivated to combine these teachings of Brusilow '91 with the teachings of Fernandes, Simell, and Blau and that the combination teaches each and every element of claim 8. (Pet. 24–26, citing Ex. 1002 ¶¶ 65–67.)

Petitioner's Ground 3 challenges claims 10 and 11. Claim 10 recites:

> **10**. The method of any of claims **1-3**, wherein the upper limit of normal blood ammonia level is 35 μmol/L.

(Ex. 1001, 26:1–2.) In regard to claim 10, Petitioner cites to the '859 Publication as teaching that the upper limit of normal for blood ammonia levels in certain clinical tests was between 26 and 35 μmol/L. (Pet. 28, citing Ex. 1008 ¶ 94.) Petitioner argues that this teaching, along with the teachings of Fernandes, Simell, and Blau, renders obvious claim 10 of the '215 patent. (Pet. 28–29, citing Ex. 1002 ¶ 73.)

Claim 11 recites:

> **11**. The method of claim **5**, further comprising:
> d) 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%.

(Ex. 1001, 26:3–7.) In regard to claim 11, Petitioner cites to Fernandes as teaching treatment of a patient with a PAA prodrug[5] (such as phenylbutyrate) (Ex. 1011, 219–20) and to the '859 Publication for its teaching that PAA prodrugs have a conversion rate of 60–75% into urinary PAGN (*see* Ex. 1008 ¶¶ 20, 43, and 223). Petitioner argues that these teachings, along with the teachings of Fernandes, Simell, and Blau, render obvious claim 11 of the '215 patent. (Pet. 29–30, citing Ex. 1002 ¶ 77.)

Petitioner's Ground 4 challenges claims 2, 4–7, 9, and 10 of the '215 patent. Claim 2 recites:

> **2**. A method of administering a nitrogen scavenging drug to a subject having a nitrogen retention disorder comprising:

[5] Dr. Sondheimer testifies that phenylbutyrate is a prodrug of phenylacetic acid ("PAA"), meaning that phenylbutyrate is converted into PAA in the body. Dr. Sondheimer testifies further that PAA, in turn, is converted to phenylacetyl glutamine ("PAGN"), which removes two ammonia ions as it is excreted from the body. (Ex. 1002 ¶ 21.) Patent Owner has not contested Dr. Sondheimer's testimony at this stage of the proceeding.

> 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 the nitrogen scavenging drug to the subject if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.

(Ex. 1001, 24:40–47.) In regard to claim 2, Petitioner cites Brusilow '84, along with Fernandes, Blau, and Simell. (Pet. 30–36.) Petitioner argues that Brusilow '84 teaches treatments for increased blood ammonia levels in children with UCDs. (Pet. 30–31, citing Ex. 1004, 1631.) According to Dr. Sondheimer, those of skill in the art would have understood the description of treatment of a patient with UCD in Brusilow '84 as measuring the blood ammonium level after a 24-hour fast. (Ex. 1002 ¶ 79.) Dr. Sondheimer testifies further that Brusilow '84 teaches comparing these fasting blood ammonia levels to the upper limit of normal for blood ammonia, and administering a dose of sodium benzoate and phenylacetate if the measured blood ammonia level is greater than half the upper limit of normal. (*Id.*) Petitioner relies on the testimony of Dr. Sondheimer to argue that those of skill in the art would have combined this teaching with the teachings of Fernandes, Simell, and Blau and would have considered the method of claim 2 to have been obvious. (Pet. 32–36, citing Ex. 1002 ¶ 96.)

Claims 4–7, 9 and 10 of the '215 patent provide further limitations on the methods of claims 1–3, including: limiting the type of nitrogen retention disorder being treated (claim 4), limiting the type of nitrogen scavenging (claims 5 and 6), adding a step of determining the upper limit of normal blood ammonia level for the subject (claim 9), and defining the upper limit of normal (claim 10). (Ex. 1001, 24:58–26:2.) At this point in the

proceeding, Petitioner shows sufficiently that each of these additional elements is taught in the cited references. (*See, e.g.,* Ex. 1004, 1631, Ex. 1011, 219, et al.)

In response to Petitioner's challenges in Grounds 2–4, Patent Owner asserts only that Brusilow '84 and Brusilow '91 do not cure the deficiencies of Fernandes, Blau, and Simell. According to Patent Owner, Fernandes, Blau, and Simell do not "draw a line" for adjusting nitrogen scavenging drug dosage when the fasting blood ammonia level is greater than half the upper limit of normal. (Prelim. Resp. 30–34.)

As discussed above, at this point in the proceeding, we find that the combined teachings of Fernandes, Blau, and Simell suggest administering a drug when the fasting blood ammonia level is greater than half the upper limit of normal. Therefore, Petitioner meets the threshold for institution of review of the claims of the '215 patent challenged in Grounds 2–4 of the Petition. We do not make a final determination of the patentability of the claims challenged in Grounds 2–4 at this time.

C. Grounds 5 and 6

Petitioner's Grounds 5 and 6 challenge claims 8 and 11, respectively, citing Brusilow '84, in addition to the references cited in Grounds 2 and 3. (Pet. 38–42.) Petitioner cites Brusilow '84 for its "broader understanding of the treatment of UCD patients with nitrogen scavenging drugs." (Pet. 38–39, citing Ex. 1002 ¶ 98.) We are not persuaded that the addition of Brusilow '84 to the references cited in Grounds 2 and 3 is necessary as a separate grounds of challenge because Petitioner has provided only broad statements, without reference to specific teachings, about how Brusilow '84 contributes to these grounds of challenge. Accordingly, we decline to

institute review based on Grounds 5 and 6. *See* 35 U.S.C. § 314(a) (institution is discretionary, not mandatory); 37 C.F.R. § 42.108(a) (Board has discretion to institute review "on all *or some* of the grounds of unpatentability asserted for each claim) (emphasis added); 37 C.F.R. § 42.1(b) (providing that the rules governing trial practice and procedure are to be construed "to secure the just, speedy, and inexpensive resolution of every proceeding.").

D. Grounds 7–9

In Ground 7, Petitioner argues that claims 1–7 and 9 are unpatentable over the combination of Scientific Discussion, Blau, and Dixon. (Pet. 43–48.) Petitioner cites Scientific Discussion for its teaching of dosing sodium phenylbutyrate (called "Ammonaps") in patients with UCDs according to individual titration and therapeutic monitoring. (Pet. 43, citing Ex. 1009, 8.) Petitioner also cites Scientific Discussion for teaching measuring plasma ammonia levels and comparing them to the upper limit of normal as part of therapeutic monitoring. (Pet. 43, citing Ex. 1009, 10.)

Petitioner relies on the testimony of Dr. Sondheimer to argue that the prior art teaches higher levels of ammonia in the blood require increasing sodium phenylbutyrate dosage and that those of skill in the art would have understood that if the ammonium value is greater than one half the upper limit of normal, sodium phenylbutyrate should also be increased. (Pet. 48, citing Ex. 1002 ¶ 116.)

Petitioner presents Scientific Discussion for teachings that are similar to those for which Petitioner cited Fernandes in Grounds 1-4. Accordingly, we do not institute review on Grounds 7-9 because the issues to be resolved

regarding the challenges to Patent Owner's claims will be resolved in regard to Grounds 1-4. 37 C.F.R. § 42.1(b).

E. Real Party-in-Interest

Petitioner identifies Par Pharmaceutical, Inc. ("Par Inc.") as the real party-in-interest. (Pet. 6.) We note that Petitioner represents that Par Inc. is a wholly owned subsidiary of Par Pharmaceutical Companies, Inc., but does not identify Par Pharmaceutical Companies, Inc. as a real party-in-interest. (Pet. 6, n.2.)

Patent Owner argues that Par Pharmaceutical Companies, Inc. ("Par Co.") was not properly identified as a real party-in-interest. (Prelim. Resp. 40.) Patent Owner argues that because of this deficiency, the Petition violates the statutory and regulatory requirements for receiving a filing date, citing 35 U.S.C. § 312(a) and 37 C.F.R. § 42.8(b)(1). Patent Owner argues further that because the Petition was filed exactly one year after Par Inc. was served with the complaint in litigation in the Eastern District of Texas, Petitioner cannot correct the failure to name all the real parties-in-interest by filing a new petition. (Prelim. Resp. 40–41.)

According to Patent Owner, Par Co. is a real party-in-interest to the proceeding because it is involved in developing, manufacturing, and distributing pharmaceutical products. (Prelim. Resp. 43–45, citing Exs. 2003 and 2004.) Patent Owner also directs us to information that, in a different proceeding, Par Co. pleaded guilty pursuant to an agreement with the United States Attorney for the District of New Jersey, and agreed to perform certain actions on behalf of Petitioner. (Prelim. Resp. 45–46, citing Ex. 2007.)

In addition, Patent Owner cites to a Securities and Exchange Commission (SEC) filing that defines the term "we" as including Petitioner and Par Co. (Prelim. Resp. 46–47, citing Ex. 2004, 8.) Patent Owner also cites to the statement in the SEC filing that "[o]n April 29, 2015, we filed Inter Partes Review petitions seeking institution of a trial on invalidity at the U.S. Patent and Trademark Office for both of the patents asserted in the Texas litigation [the '215 patent and patent 8,642,012]." (Ex. 2004, 36; *see* Prelim. Resp. 46–47.) Patent Owner argues that the use of "we" in this statement was a deliberate indication that the current Petition was filed at the behest of Par Co. (Prelim. Resp. 48–49.)

Finally, Patent Owner asserts that Thomas J. Haughey is the General Counsel and CAO of both Par Co. and Par Inc. and is also the President of Par Inc., indicating the unified nature of the relationship between Par Co. and the Petitioner. (Prelim. Resp. 50–51, citing Exs. 2008, 70, and 2009.)

On this record, we are not persuaded that Petitioner failed to name all the real parties-in-interest. Specifically, the use of the term "we" in an SEC filing, even if used deliberately when referring to what could be the current Petition, does not establish adequately that Par Co. has control over this proceeding. Nor does the evidence show that Par Co. exerts control over this proceeding merely because Par Co. and Petitioner are in a similar business and the same person has roles in both Par Co. and Par Inc. Similarly, evidence of control in a different, unrelated litigation is not evidence of Par Co.'s role in this proceeding. Instead, Patent Owner has failed to provide us with evidence of actual control by an unnamed entity sufficient to indicate that Petitioner failed to name all real parties-in-interest. *See Taylor v. Sturgell*, 553 U.S. 880, 893–95 (2008).

III. CONCLUSION

We institute an *inter partes* review of claims 1–11 of the '215 patent based on Grounds 1–4. Our findings and conclusions are not final and may change upon consideration of the whole record developed during trial.

IV. ORDER

For the reasons given, it is

ORDERED that an *inter partes* review is instituted as to claims 1, 3–7, and 9–11 under 35 U.S.C. § 103 over Fernandes, Blau, Simell, and the '859 Publication;

FURTHER ORDERED that an *inter partes* review is instituted as to claim 8 under 35 U.S.C. § 103 over Fernandes, Blau, Simell, and Brusilow '91;

FURTHER ORDERED that an *inter partes* review is instituted as to claim 2, 4–7, 9, and 10 under 35 U.S.C. § 103 over Fernandes, Brusilow '84, Blau, and Simell;

FURTHER ORDERED that no *inter partes* review is instituted on any other grounds;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '215 Patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

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