Electronic Patent Application Fee Transmittal	
Application Number:	12350111
Filing Date:	07-Jan-2009
Title of Invention:	METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Filer:	Patrick D. Morris/Colleen Kirchner
Attorney Docket Number:	643982000100
Filed as Large 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:				
Extension-of-Time:				

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12350111
Filing Date	2009-01-07
First Named Inventor	Bruce SCHARSCHMIDT
Art Unit	1651
Examiner Name	Tiffany Maureen GOUGH
Attorney Docket Number	79532.8001.US01

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					

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS Remove

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

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

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12350111
	Filing Date	2009-01-07
	First Named Inventor	Bruce SCHARSCHMIDT
	Art Unit	1651
	Examiner Name	Tiffany Maureen GOUGH
	Attorney Docket Number	79532.8001.US01

	1	DIAZ, G.A., et al., "Phase 3 Blinded, Randomized, Crossover Comparison of Sodium Phenylbutyrate (NaPBA) and Glycerol Phenylbutyrate (GPB): Ammonia (NH3) Control in Adults with Urea Cycle Disorders (UCDs)," Mol. Genet. Metab. 102:276, Society of Inherited Metabolic Disease (SMID) Abstract.	☐
	2	GHABRIL, M., et al., "Glycerol Phenylbutyrate (GPB) Administration in Patients with Cirrhosis and Episodic Hepatic Encephalopathy (HE)," accepted for presentation at Digestive Disease Week, 2012.	☐
	3	LEE, B., 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. 100:221-228 (2010).	☐
	4	LICHTER-KONECKI, U., et al., "Ammonia Control in Children with Urea Cycle Disorders (UCDs); Phase 2 Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate," Mol. Genet. Metab. 103:323-329 (2011).	☐
	5	MCGUIRE, B. M., et al., "Pharmacology and Safety of Glycerol Phenylbutyrate in Healthy Adults and Adults with Cirrhosis," Hepatology 51:2077-2085 (2010).	☐

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

EXAMINER SIGNATURE

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	12350111
	Filing Date	2009-01-07
	First Named Inventor	Bruce SCHARSCHMIDT
	Art Unit	1651
	Examiner Name	Tiffany Maureen GOUGH
	Attorney Docket Number	79532.8001.US01

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.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

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)	2012-02-22
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.**

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 the Freedom of Information Act requires disclosure of these record s.

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 inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/350,111	01/07/2009	Bruce SCHARSCHMIDT	643982000100	6290

34055 7590 03/23/2012

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

EXAMINER	
GOUGH, TIFFANY MAUREEN	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
03/23/2012	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

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 12/350,111	**Applicant(s)** SCHARSCHMIDT, BRUCE
	Examiner TIFFANY GOUGH	**Art Unit** 1651

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

THE REPLY FILED 21 February 2012 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance;

(2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.

Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because

a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);

b) ☐ They raise the issue of new matter (see NOTE below);

c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☒ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

STATUS OF CLAIMS

14. The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: .

Claim(s) objected to: .

Claim(s) rejected: 1,2,4,6-8,11,30-35,37-39, 41-45.

Claim(s) withdrawn from consideration: .

/Ruth A. Davis/
Primary Examiner, Art Unit 1651

Continuation of 11. does NOT place the application in condition for allowance because: Applicants claim amendments , particularly claims 1, 6, 7, 8 and 38 require further search and consideration as the new claim amendments have not been previously considered. The claim amendments significantly alter applicants previously claimed invention. While applicants affidavit and other evidence has been considered, the newly claimed invention requires a new search and consideration.

DO NOT ENTER
/TMG Examiner 1651/
3/19/2012

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **SCHARSCHMIDT, Bruce** **Serial No.:** 12/350,111 **Filed:** January 7, 2009 **For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS**	**Examiner:** GOUGH, Tiffany Maureen **Group Art Unit:** 1651 **Docket No.:** 79532.8001.US01 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 21st day of February 2011 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 Final Office Action mailed November 18, 2011 for the above-identified application.

Amendments to the claims begin on page 2.

Remarks begin on page 6.

Conclusion begins on page 16.

Electronic Acknowledgement Receipt

EFS ID:	12521589
Application Number:	12350111
International Application Number:	
Confirmation Number:	6290
Title of Invention:	METHODS OF TREATMENT USING AMMONIA-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:	643982000100
Receipt Date:	11-APR-2012
Filing Date:	07-JAN-2009
Time Stamp:	18:15:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$745
RAM confirmation Number	10338
Deposit Account	502586
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	SEAssertion.pdf	16285 185634517f7386014a0d255ea47d7c467f6b1149	no	1
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	RCE.pdf	627091 b4a702d8734d31dccfbc492e8f6ad661e39b4f2b	no	3
Warnings:					
Information:					
3	Extension of Time	ExtofTime.pdf	13290 fabe5f0d6212020599e2b512fedbce9201000122	no	1
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32337 b1d127a9646fb41929e7532604ac36d2ff9b5ed8	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	689003		

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 Application of: Bruce SCHARSCHMIDT	Confirmation No.: 6290
Application No.: 12/350,111	Art Unit: 1651
Filed: January 7, 2009	Examiner: Tiffany Maureen GOUGH

For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

PETITION FOR TWO-MONTH EXTENSION OF TIME

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

Sir:

Applicant petitions for a Two-Month Extension of Time in which to respond to the outstanding Final Office Action mailed November 18, 2011, extending the period for response to April 19, 2012.

☒ Fee (37 CFR § 1.17(a) (2)): ☒ Small Entity: $280.00.

☒ The Commissioner is hereby authorized to charge the requisite fee to Deposit Account No. 50-2586.

☒ Applicant petitions for an additional Extension of Time if necessary for timely filing of this petition and enclosures.

☒ Please charge any underpayment for timely consideration of this paper to Deposit Account No. 50-2586.

Respectfully submitted,
Perkins Coie LLP

Date: April 11, 2012

/Patrick D. Morris/
Patrick D. Morris, Ph.D.
Registration No. 53,351

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P.O. Box 1208
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Phone: (310) 788-9900
Fax: (206) 332-7198

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/350,111	01/07/2009	

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))							
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT 04/11/2012	(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))	* 25	Minus	** 29	= 0	X $30 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 3	Minus	***12	= 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))						225	OR		
					TOTAL ADD'L FEE	225	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		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:
/FLORENCE PATTERSON/

Electronic Patent Application Fee Transmittal

Application Number:	12350111
Filing Date:	07-Jan-2009
Title of Invention:	METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Filer:	Patrick D. Morris/Colleen Kirchner
Attorney Docket Number:	643982000100

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:				
Extension-of-Time:				
Extension - 2 months with $0 paid	2252	1	280	280

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	2801	1	465	465
		Total in USD ($)		**745**

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 04/13/2012

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Docket No.: 79532.8001.US01
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Bruce SCHARSCHMIDT	Confirmation No.: 6290
Application No.: 12/350,111	Art Unit: 1651
Filed: January 7, 2009	Examiner: Tiffany Maureen GOUGH

For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

ASSERTION OF SMALL ENTITY STATUS 37 C.F.R. § 1.27(C)(1)

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

Commissioner:

The above-identified patent application was filed as a large entity. Following a determination under 37 C.F.R §§ 1.27(a) and (f), the undersigned attorney of record states that the application is now entitled to small entity status due to the assignment of the application from Ucyclyd Pharma, Inc. to Hyperion Therapeutics, Inc. The assignment was recorded on April 9, 2012, at reel 028014, frame 0894.

Respectfully submitted,

Perkins Coie LLP

Dated: April 11, 2012

/Patrick D. Morris/
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PTO/SB/30EFS (05/07)
Approved for use through 11/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12/350,111	Filing Date	2009-01-07	Docket Number (if applicable)	79532.8001.US01	Art Unit	1651
First Named Inventor	Bruce Scharschmidt			Examiner Name	Tiffany Maureen Gough		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☒ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☒ Other Amendment and Response to Final Office Action and Declaration of Bruce Scharschmidt filed February 21, 2011

☐ Enclosed

☐ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 502586

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

Signature of Registered U.S. Patent Practitioner			
Signature	/Patrick D. Morris/	Date (YYYY-MM-DD)	2012-04-11
Name	Patrick D. Morris	Registration Number	53351

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 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.

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

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 the Freedom of Information Act requires disclosure of these record s.

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 inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

12350111 - GAU: 1651

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12350111
Filing Date	2009-01-07
First Named Inventor	Bruce SCHARSCHMIDT
Art Unit	1651
Examiner Name	Tiffany Maureen GOUGH
Attorney Docket Number	79532.8001.US01

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EFS Web 2.1.17

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TG/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12350111 12350111 - GAU: 1651
	Filing Date	2009-01-07
	First Named Inventor	Bruce SCHARSCHMIDT
	Art Unit	1651
	Examiner Name	Tiffany Maureen GOUGH
	Attorney Docket Number	79532.8001.US01

	1	DIAZ, G.A., et al., "Phase 3 Blinded, Randomized, Crossover Comparison of Sodium Phenylbutyrate (NaPBA) and Glycerol Phenylbutyrate (GPB): Ammonia (NH3) Control in Adults with Urea Cycle Disorders (UCDs)," Mol. Genet. Metab. 102:276, Society of Inherited Metabolic Disease (SMID) Abstract. 2011	☐
	2	GHABRIL, M., et al., "Glycerol Phenylbutyrate (GPB) Administration in Patients with Cirrhosis and Episodic Hepatic Encephalopathy (HE)," accepted for presentation at Digestive Disease Week, 2012.	☐
	3	LEE, B., 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. 100:221-228 (2010).	☐
	4	LICHTER-KONECKI, U., et al., "Ammonia Control in Children with Urea Cycle Disorders (UCDs); Phase 2 Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate," Mol. Genet. Metab. 103:323-329 (2011).	☐
	5	MCGUIRE, B. M., et al., "Pharmacology and Safety of Glycerol Phenylbutyrate in Healthy Adults and Adults with Cirrhosis," Hepatology 51:2077-2085 (2010).	☐

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

EXAMINER SIGNATURE

Examiner Signature	/Tiffany Gough/	Date Considered	06/13/2012

*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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TG/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/350,111	01/07/2009	Bruce SCHARSCHMIDT	643982000100	6290

34055 7590 06/18/2012

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

EXAMINER	
GOUGH, TIFFANY MAUREEN	
ART UNIT	**PAPER NUMBER**
1651	

NOTIFICATION DATE	DELIVERY MODE
06/18/2012	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)	
	12/350,111	SCHARSCHMIDT, BRUCE	
	Examiner	Art Unit	
	TIFFANY GOUGH	1651	

-- 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 *4/11/12 and 2/21/12*.

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) *1,2,4,6-8,11,30-35,37-39 and 41-45* 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) *1,2,4,6-8,11,30-35,37-39 and 41-45* is/are rejected.

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

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

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).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ 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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/22/2012*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/11/2012 has been entered. Applicants Declaration filed 2/21/2012 and IDS filed 2/22/2012 have been entered and considered.

Claims 1, 2, 4, 6-8, 11, 30-35, 37-39, 41-45 are pending and have been considered on the merits herein.

Withdrawn Rejections

The previous rejection of claims 1-4, 6-8, 10, 11, 30-44 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 13061509 is withdrawn in light of applicants filing of Express Abandonment of 13061509 on 2/29/2012.

The previous rejections under 35 U.S.C. 102(b) as being anticipated by the Brusilow references are withdrawn in light of applicants claim amendments.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to a method comprising steps (a) and (b) which are mental steps and are drawn to calculating and determining based on arbitrary amounts. The "target" outputs are whatever one of skill wants them to be and there is no claimed means to characterize the arbitrary amounts, therefore any value applies. These steps are considered to be non-limitations and mental steps. Further, the "wherein the effective initial dosage is calculated based on a mean conversion…" would involve nothing more than looking up a conversion and dosage on a graph. The claim as a whole is drawn to laws of nature and simply tells one to determine, in some manner, an arbitrary target PAGN output based upon an arbitrary target nitrogen output and using unpatentable laws of nature to calculate an effective initial dosage, i.e. reconsider drug dosage, in light of natural laws and since these non-limitations add nothing specific to laws of nature other than what is well-understood, routine and conventional activity previously engaged by those in the field, the effect is simply to tell one to apply laws of nature, somehow, with some amount when treating patients. There is no actual active step in applicants claimed invention. The term "determining" in the claim is used as a highly general language using any process such as a mental step or those which are well-known, routine and conventional in the art to

correlate an arbitrary amount to another. See 101 USPQ2d 1961 Mayo Collaborative Services v. Prometheus laboratories Inc.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to (a) determining a target PAGN output based on a target nitrogen output and calculating an effective initial dosage. Insertion of the limitation "…determining a target PAGN output based on a target nitrogen output and calculating an effective initial dosage" does not have support in the as-filed specification. The insertion of this limitation is **a new concept** because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genus which would show possession of the concept of the use of determining a target PAGN output based on a target nitrogen output and calculating an effective initial dosage. This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic

concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate possession of a concept after the fact. Thus, the insertion of "…determining a target PAGN output based on a target nitrogen output and calculating an effective initial dosage" is considered to be the insertion of new matter for the above reasons.

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, 2, 4, 6-8, 11, 30-35, 37-39, 41-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of Brusilow (Ped. Res., 1991), Brusilow (1995), and Brusilow et al. (Metabolism, 1993) in view of ClinicalTrial.gov archi (NCT0055120, 2007), Kasumov et al (Drug Metab., and Disp, 2004) and Brusilow (US6083984, US5968979).

Applicant claims a method to determine an effective dosage of a phenylacetic acid (PAA) prodrug selected from phenylbutyric acid (PBA) or a pharmaceutically

acceptable salt thereof for a patient in need of treatment for a nitrogen retention disorder, i.e. urea cycle disorder, comprising (a) determining a target PAGN output based upon a target nitrogen output and (b) calculating an effective initial dosage of PAA prodrug that results in the target urinary PAGN output, wherein the effective initial dosage is calculated based on a mean conversion of PAA prodrug to urinary PAGN of 60-75%. Applicant further claims administering the effective initial dosage to a patient.

Brusilow ('91) teaches a method to determine an effective dosage of a phenylacetic acid (PAA) prodrug selected from phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof for a patient in need of treatment for a nitrogen retention disorder, i.e. urea cycle disorder, which comprises monitoring the effect of a dosage of the prodrug in a patient to whom the prodrug has been administered, wherein monitoring the effect comprises determining the patient' s urinary phenylacetyl glutamine (PAGN) output; and determining from the urinary PAGN output adjust the effective dosage of the prodrug to produce a desired ammonia scavenging effect (abstract, p. 147, whole page-p. 149, tables 2, 3, results and discussion section, see entire document). Brusilow teaches calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into PAGN of about 80% and calculating the dosage of the PAA prodrug based on multiple factors including the patient's dietary protein intake and the patient's residual urea synthesis capacity as well as a patients dietary nitrogen (results section, p. 148, whole page, p. 149, 5th paragraph). Brusilow also teach measuring urinary creatinine in addition to urinary PAGN (p. 148, 2nd column, 1st full paragraph). Brusilow determine an effective dosage of sodium

phenylbutyrate for treating and maintaining UCD's based on PAGN conversion. Brusilow teach that the appropriate does will be a function of dietary nitrogen and nitrogen retention (p. 1472nd col., 2nd paragraph, 5th paragraph, p. 149, 5th paragraph, p. 148, results section, 1st paragraph).

Brusilow ('95) teaches a method to determine an effective dosage of a phenylacetic acid (PAA) prodrug selected from phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof for a patient in need of treatment for a nitrogen retention disorder, i.e. urea cycle disorder and encephalopathy, which comprises monitoring the effect of a dosage of the prodrug in a patient to whom the prodrug has been administered, wherein monitoring the effect comprises determining the patient' s urinary phenylacetyl glutamine (PAGN) output; and determining from the urinary PAGN output adjust the effective dosage of the prodrug to produce a desired ammonia scavenging effect (p.293, p. 300, p.302-306). Brusilow teaches calculating the effect of the dosage of prodrug based on multiple factors including the patient's dietary protein intake and the patient's residual urea synthesis capacity and teach a decrease of plasma levels of ammonium (p.305). Brusilow also teach measuring urinary creatinine in addition to urinary PAGN (p. 293 last paragraph). Brusilow determine an effective dosage of sodium phenylbutyrate for treating and maintaining UCD's and encephalopathy based on PAGN conversion (p. 303-306).

Brusilow ('93) teaches a method to determine an effective dosage of a phenylacetic acid (PAA) prodrug selected from phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof for a patient in need of treatment for a nitrogen

retention disorder, i.e. urea cycle disorder, which comprises monitoring the effect of a dosage of the prodrug in a patient to whom the prodrug has been administered, wherein monitoring the effect comprises determining the patient' s urinary phenylacetyl glutamine (PAGN) output; and determining from the urinary PAGN output adjust the effective dosage of the prodrug to produce a desired ammonia scavenging effect (abstract, p.1336, p. 1337,materials and Methods, results, Discussion, see entire document). Brusilow teaches calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into PAGN of about 92% and calculating effect of the PAA prodrug based on multiple factors including the patient's dietary protein intake and the patient's residual urea synthesis capacity (p. 1337, materials and methods). Brusilow determine an effective dosage of sodium phenylbutyrate for treating and maintaining UCD's based on PAGN conversion (discussion section). Brusilow teach that the patient's ammonia levels returned to normal (p. 1337, Results section, last full paragraph). Brusilow teach measuring daily nitrogen intake and calculating dosage based upon nitrogen intake and PAGN output (p. 1337, Results section and Table 1).

Each of the Brusilow references teach a method to determine an effective dosage of a phenylacetic acid (PAA) prodrug selected from phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof for a patient in need of treatment for a nitrogen retention disorder, i.e. urea cycle disorder and encephalopathy, which comprises monitoring the effect of a dosage of the prodrug in a patient to whom the prodrug has been administered, wherein monitoring the effect comprises determining

the patient' s urinary phenylacetyl glutamine (PAGN) output; and determining from the urinary PAGN output adjust the effective dosage of the prodrug to produce a desired ammonia scavenging effect. Brusilow teaches calculating the dosage of prodrug based on measured utilization efficiency for prodrug conversion into PAGN of about 80% and calculating the dosage of the PAA prodrug based on multiple factors including the patient's dietary protein intake and the patient's residual urea synthesis capacity. Brusilow also teach measuring urinary creatinine in addition to urinary PAGN. Brusilow determine an effective dosage of sodium phenylbutyrate for treating and maintaining UCD's and encephalopathy based on PAGN conversion. Brusilow also teach measuring ammonia levels in response to the prodrug.

Brusilow does not teach the drug HPN-100, i.e. glyceryl tri(4-phenylbutyrate) or the claimed 60-75% mean conversion.

ClinicalTrial.gov archi (2007) teaches a dose-escalation safety study on glyceryl tri(4-phenylbutyrate) to treat urea cycle disorders in comparison to sodium phenylbutyrate. They teach HPN-100 as an alternative to sodium phenylbutyrate because it is odorless, tasteless, and a concentrated oil which does not contain large amounts of sodium (detailed description). They teach performing urinalysis, pharmacokinetics, i.e. study of drugs and their metabolites, pharmacodynamics, i.e., ammonium levels, urinary excretion of PAGN (Outcomes sections).

Kasumov teaches the administering of sodium phenylbutyrate to patients having nitrogen retention disorders. They teach that the metabolites of the drug are excreted in in the urine and account for variable fractions of the dose (abstract). They teach the 50% of the administered drug is excreted in the urine (p. 10, 2nd col. 1st paragraph) and that there is variation ranging from 50% to 90% of the ingested dose (p. 16, 2nd paragraph, Table 1).

Brusilow '984 and '979 teach convenient doses of a new form of prodrug for phenylacetate. The drugs are disclosed as being used for treating diseases of nitrogen accumulation such as urea cycle disorders and encephalopathy. Brusilow teaches that sodium phenylbutyrate is known in the art to be used for treating urea cycle disorders but provide for high dosages and daily sodium amounts (col. 1, lines 15-50, Col. 2, lines 5-34, col. 3, lines 1-60). Brusilow teach a substitution therapy to that which is known in the art which provides for more convenient dosages, eliminates the peaks and valets in drug levels and the sodium component is replaced with glycerol, which is a normal product of metabolism (col. 2, lines 25-34, col. 3, lines 1-60 of '979).

At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to use the method disclosed by Brusilow ('91, '95, '93) to determine effective dosage of either HPN-100 or PBA because the method of determining dosage based upon monitoring the urinary PAG(N) output is known and disclosed by Brusilow and Kasumov, further the art teaches a clear correlation between nitrogen intake and PAGN output. Brusilow teaches administering an effective dosage

of sodium phenylbutyrate to patients in need thereof. Further, the Clinical Trials reference teaches HPN-100 as an alternative to sodium phenylbutyrate for treating the claimed diseases as well as determining proper dosage requirements using factors such as PAG(N) output. The Brusilow patents also disclose an alternative to sodium phenylbutyrate which uses glycerol in the place of the sodium component. At the time of the claimed invention, one of ordinary skill in the art would have been motivated to use the method of Brusilow with a reasonable expectation for successfully determining an effective dosage of PBA or HPN-100 because both drugs are known to be used for treating the claimed diseases and the method of determining dosage based upon PAG(N) output it also disclosed.

Brusilow makes a very clear suggestion that PAGN synthesis is a function of the dose of the prodrug as well as dietary protein and nitrogen intake(p. 149 2nd column, 5th full paragraph, Brusilow, '91). Brusilow clearly teaches an administered dose and its related PAGN synthesis, both expected and measured. Therefore, Brusilow clearly correlate dosage with PAGN output to achieve a desired effect. Further, it should be noted that applicants claim administering a dosage, i.e. clearly a known dose, of the drug, measuring PAGN output and then administering the dose. It appears as if either applicant is missing an essential step in said claimed dosage calculation or it would be obvious to calculate a desired effective dosage based upon PAGN output of a known already administered dosage. The art of record clearly suggest the dose to be a result effective variable regarding PAGN output. Further, Clinical Trials teaches

pharmacokinetics studies, i.e. urinary PAGN output and ammonia levels, in a dose-escalation/response study.

Thus, at the time of the claimed invention it would have been obvious to one of ordinary skill in the art to use PAGN output as a variable in calculating an effective dosage to be administered to a patient in need thereof because the art of record clearly teach and suggest administering a dose of the drug and calculating PAGN output and its effect on the patient in need thereof. Thus the dose is considered to be a result effective variable regarding PAGN output and its calculation would be within the purview of one of ordinary skill in the art. Further, although the art does not teach the claimed 60-75% mean conversion, it should be noted that applicant's specification teaches a huge variation in standard deviation (see specification p. 41) , which the art of record falls in. Therefore, there is no statistical difference between what is disclosed in the art and that which is disclosed by applicant. In order to be limited to the claimed percentage and to conclude the art does not teach the claimed range, one would need to know the variance and distribution, for example. Brusilow teaches measuring for output for one patient, therefore the claimed mean does not correlate to Brusilow because no statistics are possible with a patient population of one, and thus it is difficult to compare Brusilow conversion data to applicants. However, Brusilow's value falls within applicants disclosed range considering the standard deviation. Further, Kasumov teach that there is large variance in PAGN output based on dosage input (50-90%), therefore, as suggested by the art, it varies from patient to patient and dietary considerations play a clear role in dosage calculations.

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Response to Arguments

Applicant's arguments filed 2/21/2012 have been fully considered in light of the new rejection of record but they are not persuasive.

Applicant argues that the art does not teach calculating dosage based upon a 60-75% PAGN output. Applicant argues that the dose was predetermined in the Brusilow studies. Applicant argues that Clinical Trials does not suggest dosing based upon variables measured, i.e. urinary PAGN and that they do not suggest percent conversions of prodrug into PAGN.

Brusilow makes a very clear suggestion that PAGN synthesis is a function of the dose of the prodrug (p. 149 2nd column, 5th full paragraph, Brusilow, '91). Brusilow clearly teaches an administered dose and its related PAGN synthesis, both expected and measured. Therefore, Brusilow clearly correlate dosage with PAGN output to achieve a desired effect. Further, it should be noted that applicants claim administering a dosage, i.e. clearly a known dose, of the drug, measuring PAGN output and then administering the dose. It appears as if either applicant is missing an essential step in said claimed dosage calculation or it would be obvious to calculate a desired effective dosage based upon PAGN output of a known already administered dosage. The art of

record clearly suggest the dose to be a result effective variable regarding PAGN output. Further, Clinical Trials teaches pharmacokinetics studies, i.e. urinary PAGN output and ammonia levels, in a dose-escalation/response study. Further, the art of record clearly teach a variance in PAGN output compared to initial drug dosage, see Kasumov. As stated above applicants specification disclosed a huge standard deviation comprising the PAGN output percentage disclosed in the prior art, i.e. there is no statistical difference between Brusilow and the values disclosed in the specification, given the standard deviation . Applicants data suggests a variation between patients therefore, statistical data is necessary to properly compare or discredit that which is disclosed by the prior art. One of ordinary skill in the art needs to know the variance and distribution to compare. Thus, at the time of the claimed invention it would have been obvious to one of ordinary skill in the art to use PAGN output as a variable in calculating an effective dosage to be administered to a patient in need thereof because the art of record clearly teach and suggest administering a dose of the drug and calculating PAGN output and its effect on the patient in need thereof. Thus the dose is considered to be a result effective variable regarding PAGN output and its calculation would be within the purview of one of ordinary skill in the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIFFANY GOUGH whose telephone number is (571)272-0697. The examiner can normally be reached on M-F 8-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. 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.

/Tiffany M Gough/
Examiner, Art Unit 1651

/JON P WEBER/
Supervisory Patent Examiner, Art Unit 1657

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12350111	SCHARSCHMIDT, BRUCE
	Examiner	Art Unit
	TIFFANY GOUGH	1651

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST-SEE SEARCH HISTORY REPORT	7/13/2011 updated 11/9/11, 6/12/2012	tmg
Google	7/13/2011updated 11/9/11, 6/12/12	tmg
eDAN inventor search	7/13/2011 updated 6/12/12	tmg

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/TIFFANY GOUGH/ Examiner.Art Unit 1651	

79532-8003.WO00
PDM/CDK

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PATENT DOCKETING

JUN 25 2012

PERKINS COIE LLP

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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

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

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]).

...

Supplemental Box

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

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

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

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

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

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

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

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

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

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

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

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/028620

Supplemental Box

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

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

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

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

Electronic Acknowledgement Receipt

EFS ID:	13131307
Application Number:	12350111
International Application Number:	
Confirmation Number:	6290
Title of Invention:	METHODS OF TREATMENT USING AMMONIA-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:	643982000100
Receipt Date:	28-JUN-2012
Filing Date:	07-JAN-2009
Time Stamp:	14:49:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	1443
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 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Enns.pdf	217222 5362f6c61e8309894e286bcc6da28b2583c1d937	no	11
Warnings:					
Information:					
2	Non Patent Literature	ISR_WO.pdf	398953 5763d426b44557fd539b95e2fa5b181f10f49e19	no	8
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	Supplemental_IDS_8001US01.pdf	612539 ded2fc170117f5419fdb1885b4fa9c199ee59dc8	no	4
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30589 546306d859c1d8df4f2844be5ed322d8c9c1a28c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1259303		

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronic Patent Application Fee Transmittal

Application Number:	12350111
Filing Date:	07-Jan-2009
Title of Invention:	METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Filer:	Patrick D. Morris/Colleen Kirchner
Attorney Docket Number:	643982000100

Filed as Large 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:				
Extension-of-Time:				

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12350111
Filing Date	2009-01-07
First Named Inventor	Bruce Scharschmidt
Art Unit	1651
Examiner Name	Tiffany Maureen Gough
Attorney Docket Number	79532.8001.US01

U.S.PATENTS Remove

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

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

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

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	1							☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12350111
	Filing Date	2009-01-07
	First Named Inventor	Bruce Scharschmidt
	Art Unit	1651
	Examiner Name	Tiffany Maureen Gough
	Attorney Docket Number	79532.8001.US01

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

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*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	12350111
	Filing Date	2009-01-07
	First Named Inventor	Bruce Scharschmidt
	Art Unit	1651
	Examiner Name	Tiffany Maureen Gough
	Attorney Docket Number	79532.8001.US01

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.**

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 the Freedom of Information Act requires disclosure of these record s.

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 inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **SCHARSCHMIDT, Bruce** **Serial No.:** 12/350,111 **Filed:** January 7, 2009 **For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS**	)	**Examiner:** GOUGH, Tiffany Maureen **Group Art Unit:** 1651 **Docket No.:** 79532.8001.US01

DECLARATION OF BRUCE SCHARSCHMIDT

I, Bruce Scharschmidt, M.D., have personal knowledge of the facts stated herein and, if called as a witness, would competently testify to the following:

1. All of the pending claims in the present application contain a limitation specifying that the mean conversion of PAA prodrug to urinary PAGN is 60 to 75%. As discussed in my previous declaration submitted February 21, 2012, this percent conversion is derived from a series of clinical studies in both adults and children. This conversion percentage is significantly lower than that previously reported by Brusilow.

2. The Non-Final Office Action mailed June 18, 2012 states that the present application teaches "a huge variation in standard deviation (see specification p. 41), which the art of record falls in," and that "there is no statistical difference between what is disclosed in the art and that which is disclosed by applicant."

3. The standard deviation referenced by the Office Action appears to be from the table at the bottom of page 41 in the original application. This table presents data from Example 2, in which PAA metabolism was evaluated in subjects with cirrhosis. The table shows, among other items, a mean percent conversion of HPN-100 to urinary PAGN of 79.6, 58.2, 85.0, and 68.6 in four patient groups, with standard deviations of 30.5, 29.2, 65.1, and 21.9, respectively. As noted directly above the table, the overall mean percent conversion for the four subject groups was about 75%; no standard deviation is provided for the subjects as a whole.

4. The pending claims in the present application have been amended to specify urea cycle disorder (UCD) rather than nitrogen retention disorders generally. The following table provides detailed data for PAA prodrug conversion to urinary PAGN in approximately 65 UCD patients, each of whom underwent measurement of urinary PAGN output during steady state dosing with either NaPBA or the equivalent dose (i.e., the dose which delivered the same amount of PBA) of HPN-100. These data contain both the data provided in the examples section of the present application and additional data.

	NaPBA	HPN-100	All drugs
N	65	65	130
Mean % conversion	68%	67%	67%
95% CI range	64-73%	62-71%	64-70%
99% CI range	63-74%	61-72%	63-71%

5. As shown in this table, the mean percent conversion of PAA prodrug to urinary PAGN in UCD patients was 67%, with a 95% confidence range of 64-70% and a 99% confidence range of 63-71%. These results were consistent for both sodium PBA and HPN-100, indicating that similar results would be expected for all PAA prodrugs. The 95% and 99% confidence intervals for these UCD subjects falls squarely within the range recited in the present claims, and both are well below 80% (i.e., well below the lowest percentage disclosed by Brusilow for conversion of PBA to urinary PAGN). Therefore, one of ordinary skill in the art would recognize that these data are significantly different than that disclosed by Brusilow, and that this difference is statistically and clinically meaningful.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present application or any patent issued thereon.

Date: Nov 20 2012

Bruce Scharschmidt, M.D.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **SCHARSCHMIDT, Bruce** **Serial No.:** 12/350,111 **Filed:** January 7, 2009 **For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS**	**Examiner:** GOUGH, Tiffany Maureen **Group Art Unit:** 1651 **Docket No.:** 79532.8001.US01 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 21st day of November 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 June 18, 2012 for the above-identified application.

Amendments to the claims begin on page 2.

Remarks begin on page 4.

Conclusion begins on page 10.

REMARKS

Examiner interview

Examiner Gough held a telephone interview with inventor Bruce Scharschmidt and Patrick Morris (counsel for Applicant) on November 20, 2012. During the interview, the participants discussed the content of Dr. Scharschmidt's new declaration (discussed below) and potential claim amendments. Applicant thanks the Examiner for her attendance and feedback.

Non-statutory subject matter

Rejection

The Office Action rejects claim 1 as directed to non-statutory subject matter.

Response

Applicant has canceled claim 1, rendering this rejection moot.

Written description

Rejection

The Office Action rejects claims 1 and 6 as failing to comply with the written description requirement. Specifically, the Office Action asserts that the limitation "determining a target PAGN output based on a target nitrogen output and calculating an effective initial dosage" does not have support in the specification. According to the Office Action, there is neither literal support by way of generic disclosure nor specific examples of the newly limited genus "which would show possession of the concept of the use of determining a target PAGN output based on a target nitrogen output and calculating an effective dosage."

Response

Applicant has canceled claim 1, rendering the rejection moot with regard to that claim.

With regard to claim 6, Applicant have removed the term "target nitrogen output," such that the claim now simply recites "determining a target PAGN output." As noted in the specification, urinary PAGN is well known in the art as a vehicle for removing waste nitrogen (see, e.g., paragraphs 0022 and 0023), and therefore urinary PAGN output serves as a proxy for nitrogen output.

Similar amendments have been made to dependent claims 7 and 8. These amendments are fully supported by the specification as filed. For example, paragraphs 0144 to 0148 describe an embodiment in which the dosage of a PAA prodrug is calculated based in part on an estimation of the patient's target urinary PAGN output. Similarly, paragraphs 0150 to 0155 describe an embodiment in which a suitable dosage of PAA prodrug for treating an ammonia retention disorder is determined by estimating the patient's target urinary PAGN output. In both of these embodiments, the target urinary PAGN output is calculated based on the patient's residual urea synthesis capacity and dietary protein intake.

Obviousness

Rejection

The Office Action rejects independent claims 1, 6, and 38 and dependent claims 2, 4, 7, 8, 11, 30-35, 37, 39, and 41-45 as obvious over Brusilow Pediatr Res 29:147 (1991) ("Brusilow 1991"), Brusilow Progress In Liver Diseases, Ch. 12 (1995) ("Brusilow 1995"), and Brusilow Metabolism 42:1336 (1993) ("Brusilow 1993") in view of ClinicalTrials.gov NCT0055120 (2007), Kasumov Drug Metab Dispos 32:10 (2004) ("Kasumov"), and Brusilow US Patent Nos. 6,083,984 and 5,968,979.

According to the Office Action, Brusilow 1991, Brusilow 1995, and Brusilow 1993 each teach "a method to determine an effective dosage of phenylacetic acid (PAA) prodrug selected from phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof for a patient in need of treatment for a nitrogen retention disorder," where the method comprises "monitoring the effect of a dosage of the prodrug in a patient to whom the prodrug has been administered, wherein monitoring the effect comprises determining the patient's urinary phenylacetyl glutamine (PAGN) output; and determining from the urinary PAGN output adjust the effective dosage of the prodrug to produce a desired ammonia scavenging effect" (citing Brusilow 1991 "abstract, p. 147, whole page-p. 149, tables 2, 3, results and discussion section, see entire document;" Brusilow 1995 "p. 293, p. 300, p. 302-306;" Brusilow 1993 "abstract, p. 1336, p. 1337, materials and Methods, results, Discussion, see entire document"). The Office Action asserts that Brusilow 1991 "teaches calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into PAGN of about 80%"

and that Brusilow 1993 "teaches calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into PAGN of about 92%," and further asserts that all three Brusilow references teach calculating the dosage of the PAA prodrug "based on multiple factors including the patient's dietary protein intake and the patient's residual urea synthesis capacity." Finally, the Office Action states that Brusilow 1991 and Brusilow 1995"determine an effective dosage of sodium phenylbutyrate for treating and maintaining UCD's" "based on PAGN conversion" and that "the appropriate dose will be a function of dietary nitrogen and nitrogen retention (citing Brusilow 1991 "p. 1472, 2nd col., 2nd paragraph, 5th paragraph, p. 149, 5th paragraph, p. 148, results section, 1st paragraph" and Brusilow 1995 "p. 303-306").

The Office Action acknowledges that the Brusilow references do not teach HPN-100 or, more importantly, the claimed 60-75% mean conversion. However, the Office Action states that Kasumov "teaches the administering of sodium phenylbutyrate to patients having nitrogen retention disorders" and that "50% of the administered drug is excreted in the urine (p. 10, 2nd col. 1st paragraph) and that there is variation ranging from 50% to 90% of the ingested dose (p. 16, 2nd paragraph, Table 1)." The Office Action asserts that it would have been obvious to use the method disclosed in the Brusilow references to determine an effective dosage of HPN-100 or PBA because "the method of determining dosage based upon monitoring the urinary PAG(N) output is known and disclosed by Brusilow and Kasumov, further the art teaches a clear correlation between nitrogen intake and PAGN output," and Brusilow "makes a very clear suggestion that PAGN synthesis is a function of the dosage of the prodrug as well as dietary protein and nitrogen intake."

With regard to the failure of the cited references to teach the 60-75% conversion percentage recited in the present claims, the Office Action asserts that the present application "teaches a huge variation in standard deviation (see specification p. 41), which the art of record [Brusilow references] falls in," and thus "there is no statistical difference between what is disclosed in the art and that which is disclosed by applicant." According to the Office Action, "Kasumov teach that there is large variance in PAGN output based on dosage

input (50-90%), therefore, as suggested by the art, it varies from patient to patient and dietary considerations play a clear role in dosage calculations."

The Office Action goes on to state that the present claims recite "administering a dosage, i.e. clearly a known dose, of the drug, measuring PAGN output and then administering the dose," and asserts that the claims are either "missing an essential step in said claimed dosage calculation or it would be obvious to calculate a desired effective dosage based upon PAGN output of a known already administered dosage."

Response

As stated in the Response filed February 21, 2012, Applicant acknowledges that PAA prodrugs such as sodium PBA and HPN-100 were known to be useful in the treatment of various nitrogen retention disorders at the time the present application was filed. However, contrary to the statement in the Office Action, the art did not teach "a clear correlation between nitrogen intake and PAGN output." Although the art taught that PAA prodrugs are converted to urinary PAGN following administration, it did *not* teach that the precise relationship between PAA prodrug dosage and urinary PAGN output. The present application discloses the novel finding that urinary PAGN is a more reliable biomarker than plasma PAGN for evaluating PAA prodrug dosage and that "the conversion of orally administered PBA…to PAGN to urinary PAGN is incomplete, typically about 60-75%" (Specification, paragraph 0020). As discussed in the previous Response, these results directly contradict the Brusilow references, which disclosed that PAA was nearly completely converted to urinary PAGN (with a percent conversion of 80% or greater).

The Office Action is correct that "Brusilow makes a very clear suggestion that PAGN synthesis is a function of the dosage of the prodrug as well as dietary protein and nitrogen intake." However, this "very clear suggestion" was that PAA prodrugs are converted almost completely to urinary PAGN, a suggestion which the present application has now shown to be incorrect. One of ordinary skill in the art attempting to apply the teachings of Brusilow to a PAA prodrug dosage determination would have gotten their determination wrong because they would have expected the prodrug to be completely or nearly completely converted to urinary PAGN at a conversion percentage of 80-90%.

In response to the Office Action's assertion that the standard deviation in the experimental results of the present application is so large that there is "no statistical difference" between the presently claimed range and Brusilow, Applicant submits herewith the declaration of inventor Bruce Scharschmidt. This declaration provides and discusses additional data regarding the conversion of PAA prodrugs to urinary PAGN in subjects with urea cycle disorder (UCD). The data in the declaration includes the original data provided in the examples section of the present application plus additional data. Specifically, the data in the declaration shows that the mean conversion of the PAA prodrugs sodium PBA and HPN-100 to urinary PAGN in 65 subjects with UCD was 67%, with a 99% confidence interval of 63-71% and a 95% confidence interval of 64-70%. Both the 99% and 95% confidence intervals fall squarely in the middle of the 60-75% range recited in the present claims, and lie well below the lowest percent conversion taught by Brusilow (80%). One of ordinary skill in the art would recognize that the difference between these results and those disclosed in Brusilow is both statistically and clinically meaningful; as discussed in the previous Scharschmidt declaration submitted with the Response filed February 21, 2012, small differences in PAA prodrug dosage can have large effects on drug efficacy and patient health. As such, the present claims are not obvious over Brusilow in view of the various secondary references.

The present claims have been amended to recite a UCD specifically rather than nitrogen retention disorders generally. This amendment is being made solely to conform the claim language more closely to the additional data provided in the declaration, and is made without prejudice towards seeking claims directed to other nitrogen retention disorders or to nitrogen retention disorders generally in a future continuing application.

The teachings of Kasumov are irrelevant to the conversion of PAA prodrugs into urinary PAGN in a subject with a nitrogen retention disorder. The data set forth in Kasumov was obtained by administering PBA to healthy subjects, not subjects with nitrogen retention disorders as recited in the present claims. This is important because healthy subjects generally exhibit normal glutamine levels, whereas subjects with nitrogen retention disorders exhibit elevated glutamine levels. Further, Kasumov administered PBA at no more than 25%

of normal therapeutic dosage. Thus, the data set forth in Kasumov would not have been considered predictive of urinary PAGN excretion in nitrogen retention disorder subjects at standard clinical PAA prodrug dosages.

With regard to the Office Action's assertion that the present claims are missing an essential step, Applicant again respectfully disagrees. Independent claim 6 recites a method comprising the steps of (a) determining target PAGN output, (b) calculating an effective initial dosage of PAA prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60 to 75%, and (c) administering the initial dosage. This method does not require a measurement of PAGN output prior to administering the dosage; administration of PAA prodrug occurs only after the proper initial dosage has been determined using the conversion rate disclosed herein. Independent claim 38 recites a method comprising the steps of (a) administering a first dosage of PAA prodrug; (b) determining urinary PAGN excretion; (c) determining an effective dosage of PAA prodrug based on the urinary PAGN excretion, and (d) administering the effective dosage. Like claim 6, claim 38 does not require a measurement of PAGN output prior to administering the dosage. In both cases, there is no requirement in either claim that the effective dosage of PAA prodrug be known prior to the first administration; the effective dosage is determined and administered based on the novel finding that PAA prodrug is converted to urinary PAGN at a mean conversion of 60 to 75%. As such, claims 6 and 38 both constitute a complete statement of the disclosed invention.

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: November 21, 2012

/Patrick D. Morris/
Patrick D. Morris, Ph.D.
Registration No. 53,351

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Customer No. 34055
Patent - LA
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P.O. Box 1208
Seattle, WA 98111-1208
Telephone: (310) 788-9900
Facsimile: (206) 332-7198

AMENDMENTS TO THE CLAIMS

The following complete listing of claims replaces all previous claims in the application. Applicant has amended claims 2, 4, 6-8, 11, 30, and 38 and canceled claims 1, 31-35, 37, 43, and 44.

1. (canceled)

2. (currently amended) The method of claim ~~1 or~~ 6, wherein target urinary PAGN output is determined as a ratio of the concentration of urinary PAGN to urinary creatinine.

3. (canceled)

4. (currently amended) The method of claim ~~1 or~~ 6, wherein administration of the effective initial dosage of PAA prodrug produces a normal plasma ammonia level in the patient.

5. (canceled)

6. (currently amended) A method of treating a patient having a ~~nitrogen retention disorder selected from~~ urea cycle disorder ~~and hepatic encephalopathy~~ comprising (a) determining a target urinary phenylacetyl glutamine (PAGN) output ~~based on a target nitrogen output~~; (b) calculating an effective initial dosage of a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt of PBA, wherein the effective dosage of PAA prodrug is calculated based on a mean conversion of PAA prodrug to urinary PAGN of 60% to 75%; and (c) administering the effective initial dosage of PAA prodrug to the patient.

7. (currently amended) The method of claim ~~1 or~~ 6, wherein the target PAGN ~~nitrogen~~ output takes into account the patient's dietary protein intake.

8. (currently amended) The method of claim ~~1 or~~ 6, wherein the target PAGN ~~nitrogen~~ output takes into account the patient's residual urea synthesis capacity.

9. (canceled)

10. (canceled)

11. (currently amended) The method of claim 6 [[1]], wherein the PAA prodrug is HPN-100.

12-29. (canceled)

30. (currently amended) The method of claim 6 [[1]], wherein the pharmaceutically acceptable salt of PBA is sodium PBA.

31-37. (canceled)

38. (currently amended) A method of administering a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt of PBA to a patient having a ~~nitrogen retention disorder selected from~~ urea cycle disorder ~~and hepatic encephalopathy~~ comprising (a) administering a first dosage of the PAA prodrug; (b) determining urinary phenylacetyl glutamine (PAGN) excretion following administration of the first dosage of the PAA prodrug; (c) determining an effective dosage of the PAA prodrug based on the urinary PAGN excretion, wherein the effective dosage is based on a mean conversion of PAA prodrug to urinary PAGN of 60% to 75%; and (d) administering the effective dosage to the patient.

39. (previously presented)The method of claim 38, wherein urinary PAGN excretion is determined as a ratio of the concentration of urinary PAGN to urinary creatinine.

40. (canceled)

41. (previously presented)The method of claim 38, wherein the pharmaceutically acceptable salt of PBA is sodium PBA.

42. (previously presented)The method of claim 38, wherein the PAA prodrug is HPN-100.

43. (canceled)

44. (canceled)

45. (previously presented)The method of claim 38, wherein administration of the effective dosage of PAA prodrug produces a normal plasma ammonia level in the patient.

Electronic Acknowledgement Receipt

EFS ID:	14291270
Application Number:	12350111
International Application Number:	
Confirmation Number:	6290
Title of Invention:	METHODS OF TREATMENT USING AMMONIA-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:	643982000100
Receipt Date:	21-NOV-2012
Filing Date:	07-JAN-2009
Time Stamp:	14:54:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$645
RAM confirmation Number	3184
Deposit Account	502586
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	ExtofTime.pdf	55904 c59c9fffdc42ddd795dfc037d699133dbc967648	no	1
Warnings:					
Information:					
2		OAResponse.pdf	109733 ef23c2786d691858ce490491036ee2c12dc49e03	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:					
3	Rule 130, 131 or 132 Affidavits	Scharschmidt_Declaration.pdf	117086 e14e46fcf9089e49b713cabe71c9d2ae64072c36	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30643 faa8d8878be811edb265dd378a21f8f98753c698	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	313366		

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 Application of: Bruce SCHARSCHMIDT	Confirmation No.: 6290
Application No.: 12/350,111	Art Unit: 1651
Filed: January 7, 2009	Examiner: Tiffany Maureen GOUGH

For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

PETITION FOR THREE-MONTH EXTENSION OF TIME

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

Sir:

Applicant petitions for a Three-Month Extension of Time in which to respond to the outstanding non-final Office Action mailed June 18, 2012, extending the period for response to December 18, 2012.

☒ Fee (37 CFR § 1.17(a) (2)): ☒ Small Entity: $645.00.

☒ The Commissioner is hereby authorized to charge the requisite fee to Deposit Account No. 50-2586.

☒ Applicant petitions for an additional Extension of Time if necessary for timely filing of this petition and enclosures.

☒ Please charge any underpayment for timely consideration of this paper to Deposit Account No. 50-2586.

Respectfully submitted,
Perkins Coie LLP

Date: November 21, 2012

/Patrick D. Morris/
Patrick D. Morris, Ph.D.
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Seattle, WA 98111-1208
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Electronic Patent Application Fee Transmittal

Application Number:	12350111
Filing Date:	07-Jan-2009
Title of Invention:	METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Filer:	Patrick D. Morris/Colleen Kirchner
Attorney Docket Number:	643982000100

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:				
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	645	645

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**645**

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.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/350,111	01/07/2009	Bruce SCHARSCHMIDT	643982000100	6290

34055 7590 12/12/2012

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

EXAMINER	
GOUGH, TIFFANY MAUREEN	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
12/12/2012	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

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	12/350,111	SCHARSCHMIDT, BRUCE	
	Examiner	Art Unit	
	TIFFANY GOUGH	1651	

All participants (applicant, applicant's representative, PTO personnel):

(1) *TIFFANY GOUGH*.

(2) *Pat Hillsmeyer*.

(3) *Bruce Scharschmidt*.

(4) _____.

Date of Interview: *20 November 2012*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant and his representative wished to discuss the filing of a Declaration which would present a larger patient population demonstrating the 60-75% conversion rate and address standard deviation concerns raised in the previous Office action. .

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Ruth A. Davis/ Primary Examiner, Art Unit 1651	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	12/350,111	SCHARSCHMIDT, BRUCE	
	Examiner	Art Unit	
	TIFFANY GOUGH	1651	

All participants (applicant, applicant's representative, PTO personnel):

(1) *TIFFANY GOUGH*. (3)_____.

(2) *Patrick Morris*. (4)_____.

Date of Interview: *20 September 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *6 and 38*.

Identification of prior art discussed: *n/a*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicants representative, Patrick Morris, was telephoned to discuss the Examiners Amendment attached. Specifically, the Examiner suggested amending claims 6 and 38 to limit applicants claimed prodrug conversion from "about 60% to 75%" to that which is supported by the as filed specification , i.e. about 60%. Applicants specification and data submitted in the Declaration on 11/21/2012 supports the disclosed drug conversion of about 60% in UCD patients. Patrick Morris and Applicant agreed to the claim amendments. .

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2422	424/9.2.CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/09/22 21:13
L2	5891	(urea) same (cycle)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/09/22 21:14
L3	260	l2 same (disorder)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/09/22 21:15
L4	2	l1 and l3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/09/22 21:15

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	57	(phenylacetyl) same (glutamine)	USPAT; UPAD	OR	OFF	2013/09/22 21:26
L6	2	l5 same (urinary)	USPAT; UPAD	OR	OFF	2013/09/22 21:26
L7	1792	(urea) same (cycle)	USPAT; UPAD	OR	OFF	2013/09/22 21:27
L8	76	l7 same (disorder)	USPAT; UPAD	OR	OFF	2013/09/22 21:27
L9	0	l5 and l8	USPAT; UPAD	OR	OFF	2013/09/22 21:27
L10	3	(phenylacetyl) same (glutamine).clm.	USPAT; UPAD	OR	OFF	2013/09/22 21:28
L11	4	l5 and l7	USPAT; UPAD	OR	OFF	2013/09/22 21:28

9/ 22/ 2013 9:29:41 PM
C:\ Users\ tgough\ Documents\ EAST\ Workspaces\ 13723721.wsp

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12350111	SCHARSCHMIDT, BRUCE
	Examiner	**Art Unit**
	TIFFANY GOUGH	1651

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

/TIFFANY GOUGH/ Examiner.Art Unit 1651	09/22/2013	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	12	
/JON P WEBER/ Supervisory Patent Examiner.Art Unit 1657	09/23/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12350111	SCHARSCHMIDT, BRUCE
	Examiner	**Art Unit**
	TIFFANY GOUGH	1651

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION												
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED							
424	9.2	A	6	1	K	49 / 00 (2006.01.01)								
CROSS REFERENCE(S)														
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)													
514	568	432	433											

/TIFFANY GOUGH/ Examiner.Art Unit 1651	09/22/2013	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	12	
/JON P WEBER/ Supervisory Patent Examiner.Art Unit 1657	09/23/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12350111	SCHARSCHMIDT, BRUCE
	Examiner	**Art Unit**
	TIFFANY GOUGH	1651

☐ 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	6														
2	2														
3	4														
4	7														
5	8														
6	11														
7	30														
8	38														
9	39														
10	41														
11	42														
12	45														

/TIFFANY GOUGH/ Examiner.Art Unit 1651	09/22/2013	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	12	
/JON P WEBER/ Supervisory Patent Examiner.Art Unit 1657	09/23/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

12350111 - GAU: 1651

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12350111
Filing Date	2009-01-07
First Named Inventor	Bruce Scharschmidt
Art Unit	1651
Examiner Name	Tiffany Maureen Gough
Attorney Docket Number	79532.8001.US01

U.S.PATENTS Remove

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

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

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12350111 12350111 - GAU: 1651
	Filing Date	2009-01-07
	First Named Inventor	Bruce Scharschmidt
	Art Unit	1651
	Examiner Name	Tiffany Maureen Gough
	Attorney Docket Number	79532.8001.US01

	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	/Tiffany Gough/	Date Considered	09/22/2013

*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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TG/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

12350111 - GAU: 1651

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12350111
Filing Date	2009-01-07
First Named Inventor	Bruce SCHARSCHMIDT
Art Unit	1651
Examiner Name	Tiffany Maureen GOUGH
Attorney Docket Number	79532.8001.US01

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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
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Bruce SCHARSCHMIDT
	Art Unit	1651
	Examiner Name	Tiffany Maureen GOUGH
	Attorney Docket Number	79532.8001.US01

	1	DIAZ, G.A., et al., "Phase 3 Blinded, Randomized, Crossover Comparison of Sodium Phenylbutyrate (NaPBA) and Glycerol Phenylbutyrate (GPB): Ammonia (NH3) Control in Adults with Urea Cycle Disorders (UCDs)," Mol. Genet. Metab. 102:276, Society of Inherited Metabolic Disease (SMID) Abstract. (2011)	☐
	2	GHABRIL, M., et al., "Glycerol Phenylbutyrate (GPB) Administration in Patients with Cirrhosis and Episodic Hepatic Encephalopathy (HE)," accepted for presentation at Digestive Disease Week, 2012.	☐
	3	LEE, B., 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. 100:221-228 (2010).	☐
	4	LICHTER-KONECKI, U., et al., "Ammonia Control in Children with Urea Cycle Disorders (UCDs); Phase 2 Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate," Mol. Genet. Metab. 103:323-329 (2011).	☐
	5	MCGUIRE, B. M., et al., "Pharmacology and Safety of Glycerol Phenylbutyrate in Healthy Adults and Adults with Cirrhosis," Hepatology 51:2077-2085 (2010).	☐

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EXAMINER SIGNATURE

Examiner Signature	/Tiffany Gough/	Date Considered	09/22/2013

*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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TG/

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NOTICE OF ALLOWANCE AND FEE(S) DUE

34055 7590 09/30/2013
PERKINS COIE LLP - LOS General
POST OFFICE BOX 1247
SEATTLE, WA 98111-1247

EXAMINER
GOUGH, TIFFANY MAUREEN

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/30/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/350,111	01/07/2009	Bruce SCHARSCHMIDT	643982000100	6290

TITLE OF INVENTION: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	12/30/2013

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 ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

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

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

34055 7590 09/30/2013
PERKINS COIE LLP - LOS General
POST OFFICE BOX 1247
SEATTLE, WA 98111-1247

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.
12/350,111	01/07/2009	Bruce SCHARSCHMIDT	643982000100	6290

TITLE OF INVENTION: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	12/30/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
GOUGH, TIFFANY MAUREEN	1651	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)

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

NOTE: 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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/350,111	01/07/2009	Bruce SCHARSCHMIDT	643982000100	6290

34055 7590 09/30/2013

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SEATTLE, WA 98111-1247

EXAMINER	
GOUGH, TIFFANY MAUREEN	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/30/2013

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 577 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 577 day(s).

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

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

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

Privacy Act Statement

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

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

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

Notice of Allowability	Application No. 12/350,111	Applicant(s) SCHARSCHMIDT, BRUCE	
	Examiner TIFFANY GOUGH	Art Unit 1651	AIA (First Inventor to File) Status No

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

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

1. ☒ This communication is responsive to *interview on 9/20/2013*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *2,4,6-8,11,30,38,39,41,42 and 45*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

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

   * Certified copies not received: _____.

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

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

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

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 2/22/2012,6/28/2012
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *9/20/2013* .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Tiffany M Gough/
Examiner, Art Unit 1651

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

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Patrick Morris on 9/20/2013.

The application has been amended as follows:

TO THE CLAIMS:

6. (currently amended) A method of treating a patient having a urea cycle disorder comprising (a) determining a target urinary phenylacetyl glutamine (PAGN) output (b) calculating an effective initial dosage of a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt of PBA, wherein the effective dosage of PAA prodrug is calculated based on a mean conversion of PAA prodrug to urinary PAGN of about 60% ~~to 75%~~; and (c) administering the effective initial dosage of PAA prodrug to the patient.

38. (currently amended) A method of administering a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt of PBA to a patient having a from urea

cycle disorder comprising (a) administering a first dosage of the PAA prodrug; (b) determining urinary phenylacetyl glutamine (PAGN) excretion following administration of the first dosage of the PAA prodrug; (c) determining an effective dosage of the PAA prodrug based on the urinary PAGN excretion, wherein the effective dosage is based on a mean conversion of PAA prodrug to urinary PAGN of about 60% ~~to 75%~~; and (d) administering the effective dosage to the patient.

The following is an examiner's statement of reasons for allowance: The closest prior art is considered to be the Brusilow references of record. The prior art teaches an about 80% (Brusilow '91) and about 92% (Brusilow '93) prodrug conversion of PAA to urinary PAGN when administered to patients having nitrogen retention disorders including urea cycle disorder. The prior art assumes a near 100% conversion of the drug while applicant has found that only "about 60%" of the drug is converted. Applicants Declaration filed 11/21/2012 contains data drawn to an about 60% conversion rate of PAA to urinary PAGN as disclosed in the specification, which supports applicants disclosed drug conversion in the as filed specification. Applicant discloses that urea cycle disorder patients have an "about 60%" mean conversion rate.

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 TIFFANY GOUGH whose telephone number is (571)272-0697. The examiner can normally be reached on M-F 8-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. 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.

/Tiffany M Gough/
Examiner, Art Unit 1651

/JON P WEBER/
Supervisory Patent Examiner, Art Unit 1657

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12350111	SCHARSCHMIDT, BRUCE
	Examiner	Art Unit
	TIFFANY GOUGH	1651

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	9.2	9/22/2013	tmg

SEARCH NOTES		
Search Notes	Date	Examiner
EAST-SEE SEARCH HISTORY REPORT	7/13/2011 updated 11/9/11, 6/12/2012, 9/20/2013	tmg
Google	7/13/2011updated 11/9/11, 6/12/12	tmg
eDAN inventor search	7/13/2011 updated 6/12/12,9/20/2013	tmg

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
424	9.2	9/22/2013	tmg

/TIFFANY GOUGH/ Examiner.Art Unit 1651	

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
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/350,111	01/07/2009	Bruce SCHARSCHMIDT	643982000100	6290

34055 7590 10/29/2013

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

EXAMINER	
GOUGH, TIFFANY MAUREEN	
ART UNIT	**PAPER NUMBER**
1651	

NOTIFICATION DATE	DELIVERY MODE
10/29/2013	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

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

Application No. : 12350111
Applicant : Scharschmidt
Filing Date : 01/07/2009
Date Mailed : 10/29/2013

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given 2 month(s) from the mail date of this Notice, or the time remaining from the Notice of Allowance and Fee(s) Due, whichever is longer, within which to respond.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED. **This period for reply is NOT extendable under 37 CFR 1.136(a).**

See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Joanna Black/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 12350111 **Drawings filed: 01/07/2009**

IDENTIFICATION OF DRAWING DEFICIENCIES

- [ ] There is a hole or the image thereof within the illustration. FIG(s)
- [ ] The illustration is penetrated or traversed by a solid or broken line that is not intended to be part of the drawing, such as a dark line caused by a flaw in the copying process. FIG(s)
- [ ] An ink stamp or the image thereof obscures part of the illustration. FIG(s)
- [ ] The drawing is marred by black smudges, obliterations, or fax/copier marks (for example, speckles or dots in a substantial portion of the drawing). FIG(s)
- [ ] Figure numbers are duplicated or missing. FIG(s)
- [ ] Drawing sheet or figure is missing. FIG(s)
- [ ] Numbers, letters, or reference characters in the drawing have been crossed out or are illegibly handwritten. FIG(s)
- [ ] The character of the lines, numbers, and letters is poor. FIG(s)
- [ ] The drawing's background shows that the original drawing was made on graph paper or other paper with a pattern or decoration. FIG(s)
- [ ] The FIG. number label is placed in a location that causes the drawing to be read upside down. FIG(s)
- [X] Data, a reference number, or part of the drawing is truncated or missing, or a lead line has no reference number. FIG(s) 10
- [ ] The drawing and/or the FIG. label contain(s) foreign language. FIG(s)
- [ ] This utility application contains a photograph of a view that is capable of being illustrated as a line drawing. FIG(s)
- [ ] A petition under 37 CFR 1.84(a)(2) to accept color drawings has been granted, but the brief description of the drawings in the specification does not contain (or has not been amended to contain) the paragraph required by 37 CFR 1.84(a)(2)(iii).
- [ ] This reissue application contains amended drawings that are not labeled as "Amended" as required by 37 CFR 1.173(b)(3). FIG(s)
- [ ] OTHER:
- [ ] COMMENTS:

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Bruce SCHARSCHMIDT

Confirmation No.: 6290

Application No.: 12/350,111

Art Unit: 1651

Filed: January 7, 2009

Examiner: Tiffany Maureen GOUGH

For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

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

Sir:

In response to the Notice to File Corrected Application Papers - Notice of Allowance Mailed dated October 29, 2013, applicants submit a replacement drawing for Figure 10 (1 sheet). No new matter has been added to the figure. The figure is merely a clearer image of the figure as requested in the Notice.

No fees are believed due with this response. If any fee is required, the Commissioner is authorized to charge the requisite fees to Deposit Account No. 50-2586.

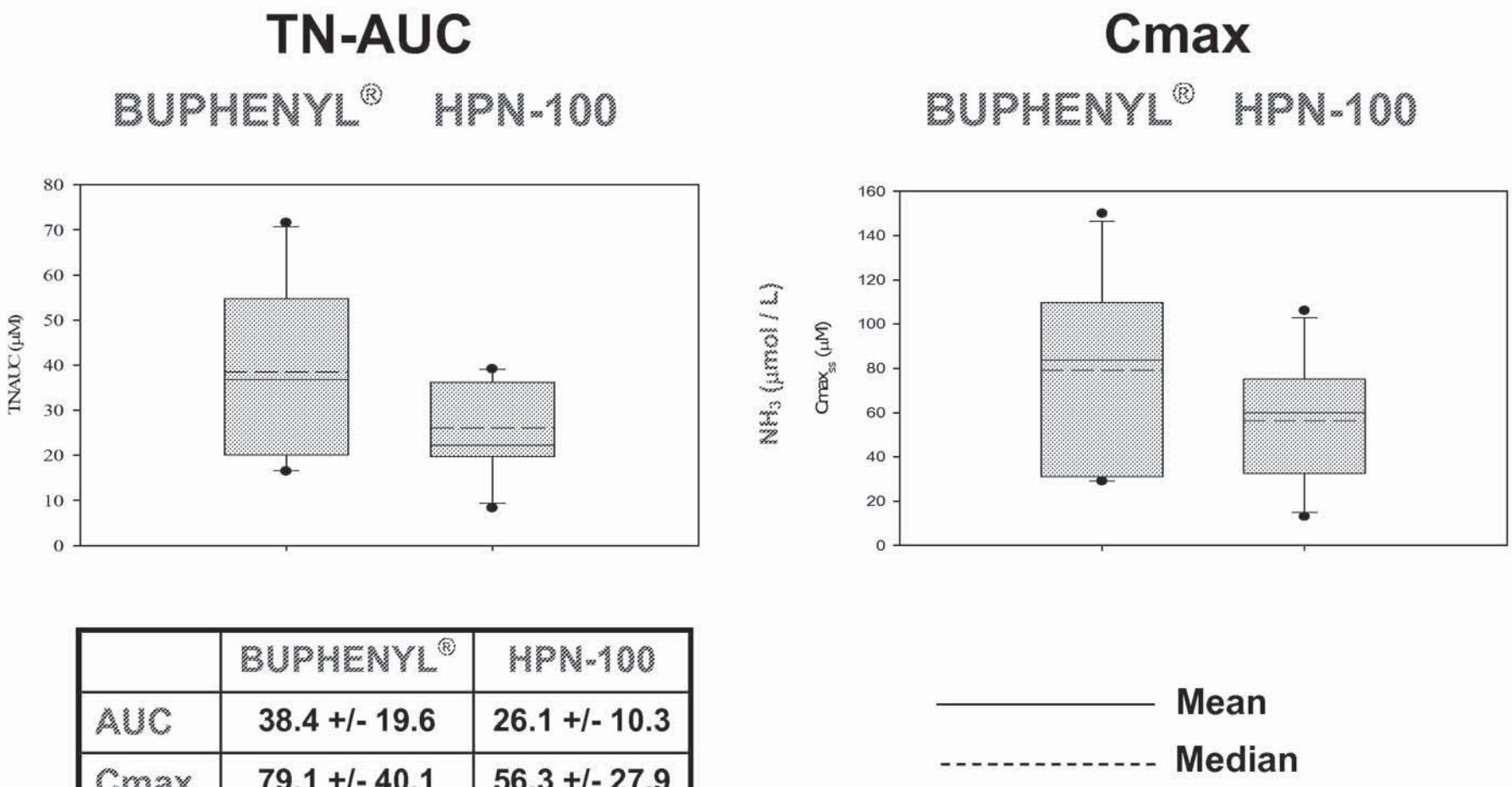
Respectfully submitted,
Perkins Coie LLP

Date: December 19, 2013

/Patrick D. Morris/
Patrick D. Morris, Ph.D.
Registration 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 10



	BUPHENYL®	HPN-100
AUC	38.4 +/- 19.6	26.1 +/- 10.3
Cmax	79.1 +/- 40.1	56.3 +/- 27.9

Electronic Acknowledgement Receipt

EFS ID:	17717678
Application Number:	12350111
International Application Number:	
Confirmation Number:	6290
Title of Invention:	METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Lara J. Dueppen/Colleen Kirchner
Filer Authorized By:	Lara J. Dueppen
Attorney Docket Number:	643982000100
Receipt Date:	19-DEC-2013
Filing Date:	07-JAN-2009
Time Stamp:	19:12:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1190
RAM confirmation Number	7841
Deposit Account	502586
Authorized User	KIRCHNER, COLLEEN

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	8001US01_IssueFeeTransmittal.pdf	1004458 f86d06f83195f939aad50a622824bc4b02fa11a5	no	2
Warnings:					
Information:					
2	Drawings-only black and white line drawings	8001US01_ReplacementDrawing.pdf	108767 997a8651048d004b30a5330397f1ffd596c065c4	no	1
Warnings:					
Information:					
3	Amendment after Notice of Allowance (Rule 312)	8001US01_Response.pdf	67706 f821f567296b0b29f86303946bb30495109946b2	no	1
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	31917 3ae18f058fd7c25a1295a43994ecafd260346326	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1212848		

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronic Patent Application Fee Transmittal

Application Number:	12350111
Filing Date:	07-Jan-2009
Title of Invention:	METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Filer:	Lara J. Dueppen/Colleen Kirchner
Attorney Docket Number:	643982000100

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	890	890
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1190**

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 09/30/2013
PERKINS COIE LLP - LOS General
POST OFFICE BOX 1247
SEATTLE, WA 98111-1247

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.

Colleen Kirchner	(Depositor's name)
/Colleen Kirchner/	(Signature)
December 19, 2013	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/350,111	01/07/2009	Bruce SCHARSCHMIDT	643982000100	6290

TITLE OF INVENTION: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	12/30/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
GOUGH, TIFFANY MAUREEN	1651	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 Patrick Morris
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 50-2586 (enclose an extra copy of this form).

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

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

NOTE: 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 December 19, 2013

Typed or printed name Patrick Morris Registration No. 53,351

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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SCORE Placeholder Sheet for IFW Content

Application Number: 12350111 Document Date: 12/19/2013

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Drawings – Other than Black and White Line Drawings

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

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At the time of document entry (noted above):

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- Other USPTO employees can bookmark the current SCORE URL (http://Score.uspto.gov/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Form Revision Date: September 30, 2013

ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	12/350,111
Filing Date	January 7, 2009
First Named Inventor	Bruce SCHARSCHMIDT
Art Unit	1651
Examiner Name	T. Gough
Attorney Docket Number	643982000100

Change(s) applied to document, /Y.Y.S./ 10/31/2013

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US ~~6,050,510~~-A 6,060,510	05-09-2000	Brusilow	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	2.	WO-2009/134460-A1	11-05-2009	Hyperion Therapeutics		
	3.	WO-2010/0250303-A1	03-04-2010	Hyperion Therapeutics		

Examiner Signature		Date Considered	

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

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	4.	AMBROSE, A.M. et al. (1933)." Further Studies on the Detoxification of Phenylacetic Acid.," *J. Biol. Chem.* 101:669-675.	
	5.	BATSHAW M.L. et al. (December 1980). "Treatment of Hyperammonemic Coma Caused by Inborn Errors of Urea Synthesis," *J. Pediatr.* 97(6):893-900	
	6.	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.	
	7.	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	
	8.	BATSHAW, M.L. (1984). "Hyperammonemia," *in* Current Problems in Pediatrics, Lockhart, J.D. ed.: Year Book Medical Publishers, pp. 2-69.	
	9.	BRUSILOW, S.W. et al. (September 1, 1979). "New Pathways of Nitrogen Excretion in Inborn Errors of Urea Synthesis," *Lancet* 2(8140):452- 454.	
	10.	BRUSILOW, S. et al. (February 8, 1980). "Amino Acid Acylation: A Mechanism of Nitrogen Excretion in Inborn Errors of Urea Synthesis," *Science* 207:659-661	
	11.	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.	
	12.	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.	
	13.	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.	

pa-1462119

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TG/

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.
12/350,111	02/04/2014	8642012	643982000100	6290

34055 7590 01/15/2014

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

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 623 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, South San Francisco, CA;

Electronic Acknowledgement Receipt

EFS ID:	18703536
Application Number:	12350111
International Application Number:	
Confirmation Number:	6290
Title of Invention:	METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Lara J. Dueppen/Colleen Kirchner
Filer Authorized By:	Lara J. Dueppen
Attorney Docket Number:	643982000100
Receipt Date:	08-APR-2014
Filing Date:	07-JAN-2009
Time Stamp:	14:11:52
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	8001US01_Request.pdf	55822 388d58ca1b00c3ccc9cdb2618f313d20294e6797	no	1

Warnings:	
Information:	

2	Miscellaneous Incoming Letter	8001US01_CertificateCorrection.pdf	60819 e11b76507aeba32edf0d9c50cf269ed054403b9f	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	116641	

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

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

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

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Bruce SCHARSCHMIDT
U.S. PATENT NO.: 8,642,012 B2
ISSUED: FEBRUARY 4, 2014
FOR: METHODS OF TREATMENT USING AMMONIA-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 8, 2014

Respectfully submitted,

PERKINS COIE LLP

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

Customer No. 34055
Perkins Coie LLP
Patent - LA
P.O. Box 1208
Seattle, WA 98111-1208
Phone: (310) 788-9900
Fax: (310) 788-3399

PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO:	:	8,642,012 B2
APPLICATION NO.	:	12/350,111
ISSUE DATE	:	February 4, 2014
INVENTOR(S)	:	Bruce SCHARSCHMIDT

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:

Column 42, line 44, claim 8, remove "from" between “having a” and “urea”.

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

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**

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,642,012 B2
APPLICATION NO.	: 12/350111
DATED	: February 4, 2014
INVENTOR(S)	: Bruce Scharschmidt

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

In the Claims

Column 42, line 44, claim 8, remove "from" between "having a" and "urea".

Signed and Sealed this
Twenty-fourth Day of June, 2014

Michelle K. Lee

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