Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				**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
Sheet	3	of	4	Attorney Docket Number	643982000100

	34.	JAMES, M.O. et al. (1972). "The Conjugation of Phenylacetic Acid in Man, Sub-Human Primates and Some Other Non-Primates Species," *Proc. R. Soc. London* 182:25-35	
	35.	JOHN, B.A. et al. (March 2009). "The Disposition of HPN-100, A Novel Pharmaceutical Under Development for Potential Treatment of Hyperammonemia, in Cynomologus Monkeys," *abstract presented at ACMG 2009*, one page.	
	36.	JOHN, B.A. et al. (March 2009). "The Disposition of HPN-100, A Novel Pharmaceutical Under Development for Potential Treatment of Hyperammonemia, in Cynomolgus Monkeys," ACMG 2009 ADME, poster, two pages.	
	37.	LEE, B. et al. (August 2009). "Dosing and Therapeutic Monitoring of Ammonia Scavenging Drugs and Urinary Phenylacetylglutamine (PAGN) as a Biomarker; Lessons From A Phase 2 Comparison of A Novel Ammonia Scavenging Agent With Sodium Phenylbutyrate (NaPBA)," *abstract presented at ICIEM 2009*, San Diego, CA, one page.	
	38.	LEE, B. et al. (August 2009). "Dosing and Therapeutic Monitoring of Ammona Scavenging Drugs and Urinary Phenylacetylglutamine (PAGN) as a Biomarker: Lessons From a Phase 2 Comparison of a Novel Ammonia Scavenging Agent with Sodium Phenylbutyrate (NAPBA)," *presented* at ICIEM 2009, San Diego, CA, poster, one page.	
	39.	LEE, B. et al. (March 2009). "Phase 2 Study of A Novel Ammonia Scavenging Agent in Adults With Urea Cycle Disorders (UCDs)," *abstract presented at ACMG 2009*, one page.	
	40.	LEE, B. et al. (March 2009). "Phase 2 Study of A Novel Ammonia Scavenging Agent in Adults with Urea Cycle Disorders (UCDs)," *presented at ACMG 2009*, seventeen pages.	
	41.	LEE, B. et al. (August 2008). "Preliminary Data on Adult Patients with Urea Cycle Disorders (UCD) in an Open-Label, Switch-Over, Dose-Escalation Study Comparing a New Ammonia Scavenger, Glyceryl Tri (4-Phenylbutyrate) [HPN -100], to Buphenyl® (Sodium Phenylbutyrate [PBA])," *abstract presented at SSIEM 2008*, Lisbon, Portugal, one page.	
	42.	LEE, B. et al. (September 2008). "Preliminary Data on Adult Patients with Urea Cycle Disorders (UCD) in An Open-Label, Switch-Over, Dose Escalation Study Comparing A New Ammonia Scavenger, Glyceryl Tri (4-Phenylbutyrate) [HPN-100], to BUPHENYL® (Sodium Phenylbutyrate [PBA]," *presented at SSIEM 2008*, Lisbon, Portugal, Poster, one page.	
	43.	LEWIS, H.B. (1914). "Studies in the Synthesis of Hippuric Acid in the Animal Organism. II. The Synthesis and Rate of Elimination of Hippuric Acid After Benzoate Ingestion In Man," *J. Biol. Chem.* 18:225-231.	
	44.	MANSOUR, A. et al. (October 1997). "Abdominal Operations in Patients with Cirrhosis: Still A Major Surgical Challenge," *Surgery* 122(4):730-735. (Abstract Only.)	
	45.	MASETRI, N.E. et al. (August 1992). "Plasma Glutamine Concentration: A Guide in the Management of Urea Cycle Disorders," *J. Pediatr.* 121(2):259-261.	
	46.	MCGUIRE, B.M. et al. (2009). "Pharmacokinetic (PK) and Safety Analyses of a Novel Ammonia-Reducing Agent in Healthy Adults and Patients with Cirrhosis," Hyperion Therapeutics, poster, one page.	
	47.	MCGUIRE, B.M. et al. (May 2009). "Pharmacokinetic (PK) and Safety Analyses of a Novel Ammonia-Reducing Agent in Healthy Adults and Patients with Cirrhosis," *abstract presented* at DDW, May 2009, two pages.	
	48.	MCGUIRE, B. et al. (April 2008). "Pharmacokinetic Safety Study of Sodium Phenylacetate and Sodium Benzoate Administered to Subjects With Hepatic Impairments,' *Liver International* 28:743. (Abstract Only).	
	49.	MCGUIRE, B. et al. (April 2008). "Pharmacokeinetic (PK) Safety Study of Sodium Phenylacetate and Sodium Benzoate Administered to Subjects with Hepatic Impairment," abstract of *The13th International Symposium*, Abano (Padova), Italy, April 28-May 1, 2008, two pages.	
	50.	MCQUADE P.S. (1984). "Analysis and the Effects of Some Drugs on the Metabolism of Phenylethylamine and Phenylacetic Acid," *Neuropsychopharmacol. Biol. Psychiat.* 8:607-614	

PAR PHARMACEUTICAL, INC.
EX. 1021
(Part 5 of 6)

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)*				***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
Sheet	4	of	4	Attorney Docket Number	643982000100

	51.	PISCITELLI, S.C. et al. (1995). "Disposition of Phenylbutyrate and its Metabolites, Phenylacetete and Phenylacetylglutamine," *J. Clin. Pharmacol.* 35:368-373.	
	52.	PROPST, A. et al. (August 1995). "Prognosis and Life Expectancy in Chronic Liver Disease," *Dig Dis Sci* 40(8):1805-1815. (Abstract Only).	
	53.	RILEY, T.R. et al. (November 15, 2001). "Preventive Strategies in Chronic Liver Disease: Part II. Cirrhosos," *Am. Fam. Physician* 64(10):1735-1740. (Abstract Only).	
	54.	SHIPLE, G.J. et al. (1922). "Synthesis of Amino Acids in Animal Organisms. I. Synthesis of Glycocoll and Glutamine in the Human Organism," *J. Am. Chem. Soc.* 44:618-624.	
	55.	SUMMAR, M.L. et al. (October 2008, e-pub. July 17, 2008). "Diagnosis, Symptoms, Frequency and Mortality of 260 Patients with Urea Cycle Disorders From a 21-Year, Multicentre Study of Acute Hyperammonaemic Episodes," *Acta Paediatr.* 97:1420-1425.	
	56.	SUMMAR, M. et al. (2007). "Description and Outcomes of 316 Urea Cycle Patients From a 21-Year, Multicenter Study of Acute Hyperammonemic Episodes," Abstract, *presented at Annual Symposium CCH – Congress Centre Hamburg*, September 4-7, 2007, GSSIEM 2007, two pages.	
	57.	SWEDISH ORPHAN INTERNATIONAL. (January 12, 2007). "Urea Cycle Disorders an International Perspective," Poster, Symposium Swedish Orphan International, Barcelona, Spain, January 12, 2007, one page.	
	58.	TUCHMAN, M. et al. (2008, e-pub. June 17, 2008). "Cross-Sectional Multicenter Study of Patients With Urea Cycle Disorders in the United States," *Molec. Genetics Metab.* 94:397-402	
	59.	WATERLOW, J.C. (March 1963). "The Partition of Nitrogen in the Urine of Malnourished Jamaican Infants," *Am. J. of Clin. Nutrition* 12:235-240.	
	60.	ZEITLIN, P.L. et al. (July 2002). "Evidence of CFTR Function in Cystic Fibrosis After System Administration of 4-Phenylbutyrate," *Mol. Therapy* 6(1):119-126	

Examiner Signature		Date Considered	

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/17 (10-08)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no person are required to respond to a collection of information unless it displays a valid OMB control number

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2009

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) $1,917.00

Complete if Known	
Application Number	12/350,111
Filing Date	January 7, 2009
First Named Inventor	Bruce SCHARSCHMIDT
Examiner Name	T. Gough
Art Unit	1651
Attorney Docket No.	643982000100

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 03-1952 Deposit Account Name: Morrison & Foerster LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fees Paid ($)
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims	- 29 or HP	Extra Claims	Fee ($)		Fee Paid ($)
24		0	x 52.00	=	0.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	- 12 or HP	Extra Claims	Fee ($)		Fee Paid ($)
3		0	x 220.00	=	0.00

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
390.00	0.00

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $270 ($135 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).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
	- 100 =		/50 =		(round **up** to a whole number) x		=	

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Deficient Fees Owed ($3,668.00 minus $1,751.00 Previously Paid)=	$1,917.00

SUBMITTED BY

Signature	/Madeline I. Johnston/	Registration No. (Attorney/Agent)	36,174	Telephone	(650) 813-5840
Name (Print/Type)	Madeline I. Johnston			Date	May 12, 2011

Docket No.: 643982000100
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bruce SCHARSCHMIDT

Application No.: 12/350,111 | Confirmation No.: 6290

Filed: January 7, 2009 | Art Unit: 1651

For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS | Examiner: T. Gough

NOTIFICATION OF LOSS OF ENTITLEMENT TO SMALL ENTITY STATUS AND PAYMENT OF DEFICIENCY FEES OWED UNDER 37 CFR 1.28(C)

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

Dear Sir:

It has come to our attention that a good faith error appears to have been made regarding the entity status of the above-referenced application and that fee payments were made in error claiming the small entity discount.

As required under 37 C.F.R. §1.28(c), to correct these oversights and in order for the error in payments to be excused, we hereby submit an itemization of all erroneous small entity payments and the differential fees, together with the deficiency payment.

pa-1454763

Itemization of all erroneous small entity payments and the differential fees:

Type of Fee	Date Paid	Amount Paid Based on Small Entity Status	Current Fee Based on Large Entity	Deficiency Amount Owed
Utility Filing Fee	January 7, 2009	$82.00	$330.00	$248.00
Utility Search Fee	January 7, 2009	$270.00	$540.00	$270.00
Utility Examination Fee	January 7, 2009	$110.00	$220.00	$110.00
Claims in Excess of 20 (9)	January 7, 2009	$234.00	$468.00	$234.00
Independent Claims in Excess of 3 (9)	January 7, 2009	$990.00	$1,980.00	$990.00
Late Oath or Declaration Fee	February 24, 2009	$65.00	$130.00	$65.00
Total of Fees		**$1,751.00**	**$3,668.00**	**$1,917.00**

Based upon the above, Applicants believe the total deficiency amount owed to be $1,917.00. Enclosed herewith is a Fee Transmittal for the purpose of charging the deficiency amount to our deposit account in the total amount of $1,917.00.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 643982000100.

Dated: May 12, 2011

Respectfully submitted,

Electronic signature: /Madeline I. Johnston/
Madeline I. Johnston
Registration No.: 36,174
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5840

pa-1454763

Docket No.: 643982000100
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bruce SCHARSCHMIDT

Application No.: 12/350,111 Confirmation No.: 6290

Filed: January 7, 2009 Art Unit: 1651

For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS Examiner: T. Gough

PETITION TO MAKE SPECIAL
UNDER 37 CFR 1.102(C)(1) - APPLICANT'S AGE

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

Dear Sir:

Submitted herewith is a Petition to Make Special the above-identified patent application on account of Applicant's age. Applicant is over 65 years of age.

Accordingly, Applicant requests that this Petition to Make Special be granted and the application undergo accelerated examination.

pa-1459560

It is Applicants' understanding that the above-referenced application for patent has not yet been examined by an Examiner at the United States Patent and Trademark Office (USPTO). Accordingly, Applicant submits this Petition to Make Special under MPEP § 708.02 IV. No Fee is due, see 37 CFR §1.102(G).

However, if it is determined that fees are due, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Deposit Account No. 03-1952** under Attorney Docket No. 643982000100.

Dated: May 12, 2011

Respectfully submitted,

E-Signature: /Madeline I. Johnston/
Madeline I. Johnston
Registration No.: 36,174
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5840

pa-1459560

PTO/SB/130 (07-09)
Approved for use through 07/31/2012. OMB 0651- 0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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

PETITION TO MAKE SPECIAL BASED ON AGE FOR ADVANCEMENT OF EXAMINATION UNDER 37 CFR 1.102(c)(1)

Application Information

Application Number	12350111	Confirmation Number	6290	Filing Date	2009-01-07
Attorney Docket Number (optional)	643982000100	Art Unit	1651	Examiner	T Gough
First Named Inventor	Bruce SCHARSCHMIDT				
Title of Invention	METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS				

Attention: Office of Petitions

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

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

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

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

Given Name	Middle Name	Family Name	Suffix
Bruce		SCHARSCHMIDT	

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

Select (1) or (2) :

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

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

Signature	/Madeline I. Johnston/	Date (YYYY-MM-DD)	2011-05-12
Name	Madeline I. Johnston	Registration Number	36174

Docket No.: 643982000100
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bruce SCHARSCHMIDT

Application No.: 12/350,111 | Confirmation No.: 6290

Filed: January 7, 2009 | Art Unit: 1651

For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS | Examiner: T. Gough

FIRST PRELIMINARY AMENDMENT UNDER 37 C.F.R. 1.115

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

Dear Sir:

Prior to examination on the merits, Applicant respectfully requests entry of this Preliminary Amendment for the above-captioned patent application.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Patent
Docket No. 643982000100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bruce SCHARSCHMIDT

Application No.: 12/350,111

Filing Date: January 7, 2009

For: METHODS OF TREATMENT USING AMMONIA-SCAVENING DRUGS

Examiner: T. Gough

Group Art Unit: 1651

Confirmation No.: 6290

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98

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

Dear Sir:

Pursuant to 37 C.F.R. §1.97 and § 1.98, Applicant submits for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a/b. Copies of foreign documents and non-patent literature are submitted herewith. The Examiner is requested to make these documents of record.

This Supplemental Information Disclosure Statement is submitted:

☐ With the application; accordingly, no fee or separate requirements are required.

☐ Before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

pa-1462999

☒ Within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements are required. ~~However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.~~

☐ After receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance.

- ☐ A fee is required. Accordingly, a Fee Transmittal Form (PTO/SB/17) is attached to this submission.
- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above; accordingly; no fee is believed to be due.

☐ After mailing of a final Office Action or Notice of Allowance, but before payment of the Issue Fee.

- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above and a Fee Transmittal Form (PTO/SB/17) is attached to this submission.

Applicant would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

The information contained in this Supplemental Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

In the unlikely event that the transmittal form is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petition and/or other

fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing 643982000100.

Dated: May 12, 2011

Respectfully submitted,

Electronic Signature: /Madeline I. Johnston/
Madeline I. Johnston
Registration No.: 36,174
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5840

PTO/SB/21 (07-09)
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 displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

		Application Number	12/350,111
		Filing Date	January 7, 2009
		First Named Inventor	Bruce SCHARSCHMIDT
		Art Unit	1651
		Examiner Name	T. Gough
Total Number of Pages in This Submission	24 + 59 refs.	Attorney Docket Number	643982000100

ENCLOSURES (*Check all that apply*)

[x] Fee Transmittal Form (1 page)	[ ] Drawing(s)	[ ] After Allowance Communication to TC
[ ] Fee Attached	[ ] Licensing-related Papers	[ ] Appeal Communication to Board of Appeals and Interferences
[x] Amendment/Reply (Preliminary, 6 pages)	[x] Petition (Petition to Make Special Under 37 CFR 1.102(C)(1)-Applicant's Age and Form PTO/SB/130, 3 pages)	[ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
[ ] After Final	[ ] Petition to Convert to a Provisional Application	[ ] Proprietary Information
[ ] Affidavits/declaration(s)	[ ] Power of Attorney, Revocation Change of Correspondence Address	[ ] Status Letter
[ ] Extension of Time Request	[ ] Terminal Disclaimer	[x] Other Enclosure(s) (please Identify below):
[ ] Express Abandonment Request	[ ] Request for Refund	**Please see "Remarks" section.**
[x] Information Disclosure Statement (Supplemental, 3 pages)	[ ] CD, Number of CD(s) _____	
[ ] Certified Copy of Priority Document(s)	[ ] Landscape Table on CD	
[ ] Reply to Missing Parts/ Incomplete Application		
[ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53		

Remarks

- Notification of Loss of Entitlement to Small Entity Status and Payment of Deficiency Fees Owed Under 37 CFR 1.28(c) (3 pages)
- Supplemental Application Data Sheet (3 pages)
- Form PTO/SB/08A/B (4 pages)
- Fifty nine (59) references

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP (Customer No. 25226)		
Signature	/Madeline I. Johnston/		
Printed name	Madeline I. Johnston		
Date	May 12, 2011	Reg. No.	36,174

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

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO CA 92130-2040

MAILED

MAY 24 2011

OFFICE OF PETITIONS

In re Application of :

SCHARSCHMIDT, Bruce :
Application No. 12/350,111 : DECISION ON PETITION
Filed: January 07, 2009 : TO MAKE SPECIAL UNDER
Attorney Docket No. **643982000100** : 37 CFR 1.102(c)(1)
:

This is a decision on the petition under 37 CFR 1.102(c)(1), filed May 12, 2011, to make the above-identified application special based on applicant's age as set forth in M.P.E.P. § 708.02, Section IV.

The petition is **GRANTED**.

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

The instant petition includes a statement by Bruce Scharschmidt attesting to his age. Accordingly, the above-identified application will be accorded "special" status.

Telephone inquiries concerning this decision should be directed to Tredelle Jackson at 571-272-2783.

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

The application is being forwarded to the Technology Center Art Unit 1651 for action on the merits commensurate with this decision.

/Tredelle D. Jackson/
Paralegal Specialist
Office of Petitions

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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BIB DATA SHEET

CONFIRMATION NO. 6290

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/350,111	01/07/2009	424	1651	643982000100

APPLICANTS
Bruce SCHARSCHMIDT, South San Francisco, CA;

**** CONTINUING DATA ***************************
This appln claims benefit of 61/093,234 08/29/2008
and claims benefit of 61/048,830 04/29/2008

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
01/21/2009

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /TIFFANY MAUREEN GOUGH/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	15	29	12

ADDRESS

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040
UNITED STATES

TITLE

METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

FILING FEE RECEIVED		
1751	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S87	3	(HPN-100) and (urea)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 12:31
S88	1	(phenylbutrate) and (urea)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 12:32
S89	892	(phenylbutyrate) and (urea)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 12:32
S90	102	(phenylbutyrate) same (urea)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 12:32
S91	0	S90 same (PAG)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 12:32
S92	13	S90 and (PAG)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 12:32
S93	27	S90 and (phenylacetylglutamine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 12:33
S94	45	(glycerol) same (phenylbutyrate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 13:13
S95	10	S90 and S94	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 13:13
S96	15	S93 and (encephalopathy)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 13:20
S97	4	S94 and S96	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 13:23
S98	13	("20040229948" | "20060135612" | "20080119554" | "4284647" | "5968979" | "6050510").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/07/13 14:08

EAST Search History (Interference)

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(Based on PTO 08-08 version)

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	12/350,111
Filing Date	January 7, 2009
First Named Inventor	Bruce SCHARSCHMIDT
Art Unit	1614
Examiner Name	Not Yet Assigned
Attorney Docket Number	643982000100

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

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NON PATENT LITERATURE DOCUMENTS

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	1.	MACARTHUR et al. (2004). Molecular Genetics and Metabolism 81(1):S67-S73	
	2.	SIMMELL et al. (1986). Pediatric Research 20(11):1117-1121	
	3.	TANNER et al. (2007). Journal of Inherited Metabolic Disease 30(5):716-721	
	4.	International Search Report and Written Opinion for PCT/US2009/055256, mailed 30 December 2009, 13 pages	

Examiner Signature	/Tiffany Gough/	Date Considered	07/14/2011

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	1.	WO-2005/053607	06/2005			
	2.	WO-2009/087474	07/2009			

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	3.	ClinicalTrials.Gov/Archive View of NCT00551200 on 2007_12_11 "Dose-Escalation Safety Study of Glyceryl Tri (4-Phenylbutyrate)(GT4P) to Treat Urea Cycle Disorders" [accessed 5 October 2009], 4 pages	
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	5.	LEE et al., Journal of Inherited Metabolic Disease (2008) 31(1):91	
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	1.	US-4,284,647	08/1981	Brusilow et al.	

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	2.	International Search Report and Written Opinion for PCT/US09/30362, mailed 2 March 2009, 8 pages	

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	1.	US-5,968,979	10/1999	Brusilow	
	2.	US-2004/0229948	11/2004	Summar et al.	
	3.	US-2006/0135612	06/2006	Ferrante	
	4.	US-2008/0119554	05/2008	Jalan et al.	

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	5.	WO-2006/056794	06/2006			

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	6.	BERRY et al., J Pediatrics (2001) 138:S56-S61	
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	16.	THIBAULT et al., Cancer Research (1994) 54(7):1690-1694	

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Sheet 1 of 4

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Application Number	12/350,111
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Examiner Name	T. Gough
Attorney Docket Number	643982000100

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	1.	US-6,050,510-A	05-09-2000	Brusilow	

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	2.	WO-2009/134460-A1	11-05-2009	Hyperion Therapeutics		
	3.	WO-2010/0250303-A1	03-04-2010	Hyperion Therapeutics		

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Sheet 2 of 4

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Filing Date	January 7, 2009
First Named Inventor	Bruce SCHARSCHMIDT
Art Unit	1651
Examiner Name	T. Gough
Attorney Docket Number	643982000100

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Examiner Name	T. Gough
Attorney Docket Number	643982000100

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pa-1462119
ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TG/

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 4 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

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Examiner Signature	/Tiffany Gough/	Date Considered	07/14/2011

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TG/

Notice of References Cited	Application/Control No. 12/350,111	Applicant(s)/Patent Under Reexamination SCHARSCHMIDT, BRUCE	
	Examiner TIFFANY GOUGH	Art Unit 1651	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,083,984	07-2000	Brusilow, Saul W.	514/533
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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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

25225 7590 07/21/2011
MORRISON & FOERSTER LLP
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SAN DIEGO, CA 92130-2040

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

NOTIFICATION DATE	DELIVERY MODE
07/21/2011	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):

EOfficeSD@mofo.com
PatentDocket@mofo.com
Drcaldwell@mofo.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 *12 May 2011*.

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

3)☐ 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

4)☒ Claim(s) *1-4,6-8,10,11 and 30-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,10,11 and 30-44* is/are rejected.

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

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

Application Papers

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

10)☐ 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).

11)☐ 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

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/24/09,6/2/09,2/2/10,4/1/10,5/12/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4, 6-8, 10, 11, 30-44 are pending and have been considered on the merits herein.

Claim Rejections - 35 USC § 102

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

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

Claims 1, 3, 6-8, 10, 30, 31, 33, 36-41, 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Brusilow (Ped. Res., 1991).

Applicant claims a method to determine an effective dosage of a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof for a patient in need of treatment for a nitrogen retention disorder selected from urea cycle disorder and hepatic 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. The method comprises calculating the dosage of prodrug based on utilization efficiency for prodrug conversion

into PAGN of about 60% to about 75%. The method comprises wherein the dosage of the PAA prodrug is calculated from the patient's dietary protein intake and the dosage of the PAA prodrug is adjusted to account for the patient's residual urea synthesis capacity. The method also claims the PAA prodrug is sodium phenylbutyrate. and the nitrogen retention disorder is urea cycle disorder.

Brusilow 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 60% to about 75% 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 (results section, p. 148, whole page). 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.

Thus, the reference anticipates the claimed subject matter.

Claims 1, 3, 6-8, 10, 30-34, 36-41, 43, 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Brusilow (1995).

Brusilow 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 dosage of prodrug based on a utilization efficiency for prodrug conversion into PAGN of about 60% to about 75% 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 (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).

Thus, the reference anticipates the claimed subject matter.

Claims 1, 3, 6-8, 10, 30, 31, 33, 36-41, 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Brusilow et al. (Metabolism, 1993).

Brusilow 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 60% to about 75% 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 (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).

Thus, the reference anticipates the claimed subject matter.

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 1-4, 6-8, 10, 11, 30-44 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) and Brusilow (US6083984, US5968979)..

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 a utilization efficiency for prodrug conversion into PAGN of about 60% to about 75%

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 does not teach the drug HPN-100, i.e. glyceryl tri(4-phenylbutyrate).

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).

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 dislosed by Brusilow. 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.

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.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-8, 10, 11, 30-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 13061507. Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are drawn to the methods of determining an effective dose of a PAA prodrug. Claim 1 of the instant invention is drawn to both PBA or HPN-100, while '507 is drawn to HPN-100 or a PAA prodrug which is either HPN-100 or PBA, for example, claims 1, 9-11.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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
/Ruth A. Davis/

Primary Examiner, Art Unit 1651

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	tmg
Google	7/13/2011	tmg
eDAN inventor search	7/13/2011	

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/350,111	01/07/2009	1651	1751	643982000100	29	12

CONFIRMATION NO. 6290

CORRECTED FILING RECEIPT

25225
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

Date Mailed: 08/02/2011

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Bruce SCHARSCHMIDT, South San Francisco, CA;

Assignment For Published Patent Application

UCYCLYD PHARMA, INC., Scottsdale, AZ

Power of Attorney: The patent practitioners associated with Customer Number 25225

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/093,234 08/29/2008

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

If Required, Foreign Filing License Granted: 01/21/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/350,111**

Projected Publication Date: Not Applicable

Non-Publication Request: No

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

Title

METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

Preliminary Class

424

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

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

Docket No.: 643982000100
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bruce SCHARSCHMIDT

Application No.: 12/350,111 | Confirmation No.: 6290

Filed: January 7, 2009 | Art Unit: 1651

For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS | Examiner: T. Gough

NOTIFICATION OF LOSS OF ENTITLEMENT TO SMALL ENTITY STATUS AND PAYMENT OF DEFICIENCY FEES OWED UNDER 37 CFR 1.28(C)

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

Dear Sir:

It has come to our attention that a good faith error appears to have been made regarding the entity status of the above-referenced application and that fee payments were made in error claiming the small entity discount.

As required under 37 C.F.R. §1.28(c), to correct these oversights and in order for the error in payments to be excused, we hereby submit an itemization of all erroneous small entity payments and the differential fees, together with the deficiency payment.

[illegible] 12350111

pa-1454763

Itemization of all erroneous small entity payments and the differential fees:

Type of Fee	Date Paid	Amount Paid Based on Small Entity Status	Current Fee Based on Large Entity	Deficiency Amount Owed
Utility Filing Fee	January 7, 2009	$82.00	$330.00	$248.00
Utility Search Fee	January 7, 2009	$270.00	$540.00	$270.00
Utility Examination Fee	January 7, 2009	$110.00	$220.00	$110.00
Claims in Excess of 20 (9)	January 7, 2009	$234.00	$468.00	$234.00
Independent Claims in Excess of 3 (9)	January 7, 2009	$990.00	$1,980.00	$990.00
Late Oath or Declaration Fee	February 24, 2009	$65.00	$130.00	$65.00
Total of Fees		**$1,751.00**	**$3,668.00**	**$1,917.00**

Based upon the above, Applicants believe the total deficiency amount owed to be $1,917.00. Enclosed herewith is a Fee Transmittal for the purpose of charging the deficiency amount to our deposit account in the total amount of $1,917.00.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 643982000100.

Dated: May 12, 2011

Respectfully submitted,

Electronic signature: /Madeline I. Johnston/
Madeline I. Johnston
Registration No.: 36,174
MORRISON & FOERSTER LLP
755 Page Mill Road
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pa-1454763

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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MAILED

AUG 19 2011

OFFICE OF PETITIONS

In re Application:	:	
Bruce Scharschmidt	:	
Application No. 12/350,111	:	ON PETITION
Filed: January 7, 2009	:	
Attorney Docket No. 643982000100	:	

This is a notice regarding your request for acceptance of a fee deficiency submission under 37 CFR 1.28 filed May 12, 2011.

On September 1, 1998, the Court of Appeals for the Federal Circuit held that 37 CFR 1.28(c) is the sole provision governing the time for correction of the erroneous payment of the issue fee as a small entity. **See DH Technology v. Synergystex International, Inc. 154 F.3d 1333, 47 USPQ2d 1865 (Fed. Cir. Sept. 1, 1998).**

The Office no longer investigates or rejects original or reissue applications under 37 CFR 1.56. **1098 Off. Gaz. Pat. Office 502 (January 3, 1989)**. Therefore, nothing in this Notice is intended to imply that an investigation was done.

Your fee deficiency submission under 37 CFR 1.28 is hereby **ACCEPTED**.

This application is no longer entitled to small entity status. Accordingly, all future fees paid in this application must be paid at the large entity rate.

The address given on the petition differs from the address of record. A courtesy copy of this decision is being mailed to the address given on the petition; however, the Office will mail all future correspondence solely to the address of record.

Telephone inquires concerning this decision should be directed to the undersigned at (571) 272-7751.

/Joan Olszewski/
Joan Olszewski
Petitions Examiner
Office of Petitions

cc: Madeline I. Johnston
Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018

Docket No.: 643982000100
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bruce SCHARSCHMIDT

Application No.: 12/350,111 | Confirmation No.: 6290

Filed: January 7, 2009 | Art Unit: 1651

For: METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS | Examiner: T. Gough

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. 1.111

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

Dear Sir:

INTRODUCTORY COMMENTS

This is in response to the non-final Office Action dated July 21, 2011 (Paper No. 20110711), for which a response is due on October 21, 2011. Accordingly, this response is timely filed. Reconsideration and allowance of the pending claims in light of the remarks presented herein are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

REMARKS

Claims 1-4, 6-8, 10, 11, 30-44 were pending in the present application. By virtue of this response, claims 3, 6, 38 and 39 have been amended to recite urinary PAGN as recited elsewhere in the claims. No claims have been cancelled. New claim 45 (dependent from claim 1) has been added. Support for the new claim may be found throughout the specification as originally filed, for example, in paragraphs [0020]-[0022]. No new matter is introduced. Accordingly, claims 1-4, 6-8, 10, 11, 30-45 are currently under consideration.

Amendment of the claims listed above is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. Moreover, it is not to be construed that Applicants have acquiesced to any rejections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

I. Examiner Interview

Applicant thanks the Examiner for her time and consideration of the remarks presented herein and for the courtesy of the in-person interview conducted on October 14, 2011. In addition to the Examiner, Applicant Dr. Bruce Scharschmidt and Applicant's representatives Catherine Polizzi and Anita Choi were present for the in-person interview. The cited references and the claims of the present application were discussed. No agreement was reached as to allowability of the claims. Applicant appreciates the observations and suggestions made by the Examiner, which are reflected in this response.

Applicant thanks the Examiner in advance for her time and consideration of the amendments and remarks presented herein. Should this response not fully address the Examiner's concerns, the Examiner is asked to contact the undersigned regarding any outstanding issues prior to the issuance of a further action on the merits.

II. Claim Rejections Under 35 USC § 102

A. Brusilow (Ped.Res., 1991)

Claims 1, 3, 6-8, 10, 30, 31, 33, 36-41, 43 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Brusilow (Ped. Res., 1991) (hereinafter "Brusilow 1991"). Applicant respectfully traverses the rejection.

Brusilow 1991 does not teach using the measurement of urinary PAGN output for the purpose of or as a basis for determining or calculating the dosage for a PAA prodrug to be administered to a patient as is currently claimed. Rather, dosage was pre-determined in the three studies performed in Brusilow 1991 based on dietary protein intake and an assumption regarding the amount of dietary intake excreted as waste nitrogen. *See* Brusilow 1991, page 147, right column, fifth paragraph. Moreover, urinary PAGN was not measured as a basis or factor to be taken into consideration to determine dosage, but rather was measured to establish that PAGN derived from phenylacetate or phenylbutyrate can account for a substantial fraction of waste nitrogen derived from dietary protein, which led to the conclusion that "PAG[N] may replace urea as a waste nitrogen product when phenylbutyrate is administered". *See* Brusilow 1991, Abstract and Title.

The Examiner cited Tables 2 and 3 in support of this rejection. Table 2 is entitled "Partition of urinary nitrogen in patient described in Table 1" and summarizes the patient's amounts of total nitrogen, urea nitrogen, and ammonium nitrogen in the three periods of the first study. Table 2 does not disclose the amount of urinary PAGN, which is the output measured and used as a basis to determine or calculate PAA prodrug dosage as recited in the pending claims, nor is the partition of urinary nitrogen as summarized in Table 2 used to determine dosage. Table 3 is entitled "Overnight fasting plasma levels of phenylbutyrate, phenylacetate, and PAG in 10 patients receiving various doses of sodium phenylbutyrate" and summarizes levels of metabolites in plasma. Table 3 does not teach measuring and determining or calculating PAA prodrug dosage based on urinary PAGN output, as recited in the pending claims.

With respect to pending claims 3, 6 and 38, Applicant respectfully disagrees with the Examiner's statement that "Brusilow teaches calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into PAGN of about 60% to about 75%". *See* page 3 of the Office Action dated July 21, 2011. There is no such percentage disclosed in Brusilow 1991. Rather, Brusilow 1991 teaches that the drug is completely, or nearly so, conjugated with glutamine to form PAGN. *See* page 149, right column, first and second paragraphs.

With respect to pending claim 2, Applicant notes that creatinine was measured as part of a calculation to determine total urinary nitrogen and completeness of urine collection in Brusilow 1991, not as a basis to determine drug dosage in conjunction with urinary PAGN, as recited in the claims. *See* page 148, right column, second and fourth paragraphs.

Therefore, claims 1, 3, 6-8, 10, 30, 31, 33, 36-41, and 43 are not anticipated by Brusilow 1991. Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 102(b).

B. Brusilow (1995)

Claims 1, 3, 6-8, 10, 30-34, 36-41, 43, 44 are rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Brusilow (1995) (hereinafter "Brusilow 1995"). Applicant respectfully traverses the rejection.

Brusilow 1995 does not teach using the measurement of urinary PAGN output for the purpose of or as a basis for determining or calculating the dosage for a PAA prodrug to be administered to a patient as is currently claimed. Brusilow 1995 is a review article in which he reiterates findings from Brusilow 1991 and Brusilow 1993 and teaches administering phenylbutyrate as a therapeutic option to increase waste nitrogen excretion. Specifically, the section of the reference entitled "Maintenance Therapy of Urea Cycle Disorders" discloses that "[i]n addition to dietary therapy, patients with deficiencies of CPS, OTC, and ASD receive oral sodium phenylbutyrate at dosages of 450 to 600 mg/kg/d". *See* Brusilow 1995, page 303. This dosage is in essence the same as the dosages reported in Brusilow 1991. This dosage was not determined based on any output, much less urinary PAGN.

Furthermore, Brusilow 1995 discloses that administering phenylbutyrate has an additional advantage of reducing urea synthesis, which "becomes available as a homeostatic reserve waste nitrogen pathway if needed". *See* page 305. In other words, Brusilow 1995 reiterates some of the findings from Brusilow 1991 and Brusilow 1993 and discloses some of the advantages associated with administering phenylbutyrate to treat nitrogen retention disorders (*e.g.*, urea cycle disorder and encephalopathy). This reference does not teach measuring urinary PAGN for the purpose of and as a basis for determining or calculating a PAA prodrug dosage as claimed.

With respect to pending claims 3, 6 and 38, Applicant respectfully disagrees that "Brusilow teaches calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into urinary PAGN of about 60% to about 75%". *See* page 4 of the Office Action dated July 21, 2011. The Examiner cited page 305 to support this statement. However, the only mention of a percentage on this page is that "urea synthesis decreased by 1.7g/day (73%) during Period 2 when phenylbutyrate was prescribed". The 73% urea synthesis decrease disclosed on page 305 refers to the reduction in urea synthesized by the patient when administered sodium phenylbutyrate as reported initially in Brusilow 1993, not the conversion of PAA prodrug into urinary PAGN.

With respect to pending claim 2 (creatinine), Applicant respectfully points out that creatinine was measured as one of several factors in the blood, not in the urine, as part of the evaluation of the patient (*see* page 293, section entitled "Composite Case"), not to determine drug dosage in conjunction with measuring urinary PAGN.

Therefore, claims 1, 3, 6-8, 10, 30-34, 36-41, 43, and 44 are not anticipated by Brusilow 1995. Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 102(b).

C. Brusilow (Metabolism, 1993)

Claims 1, 3, 6-8, 10, 30, 31, 33, 36-41, 43 are rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Brusilow et al. (Metabolism, 1993) (hereinafter "Brusilow 1993"). Applicant respectfully traverses the rejection.

Brusilow 1993 does not teach measuring urinary PAGN output to be used as a basis to determine or calculate a dosage for a PAA prodrug to be administered to a patient. Rather, dosage was pre-determined in the study performed in Brusilow 1993, based on the same assumptions provided in Brusilow 1991 (discussed above) and represents a progression of escalating dosage in a clinical study. Moreover, the outputs were not measured to be used as a factor in determining dosage, but rather were used to compare urea N synthesis and phenylacetylglutamine N synthesis under differing conditions. *See* Brusilow 1993, page 1337, Results section.

Based on the data in this study, this reference discloses that "phenylbutyrate administration led to a 73% decrease in net de novo urea N synthesis during period II". *See* Brusilow 1993, Abstract. As discussed above, urea synthesis decrease refers to the change in urea synthesized by the patient when given phenylbutyrate, not the conversion of PAA prodrug into urinary PAGN. Therefore, this reference does not teach measuring urinary PAGN for the purpose of or use as a factor in determining or calculating a PAA prodrug dosage.

With respect to pending claims 3, 6 and 38, Applicant respectfully disagrees that "Brusilow teaches calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into urinary PAGN of about 60% to about 75%". *See* page 5 of the Office Action dated July 21, 2011. The Examiner cited page 1337 (Materials and Methods) to support this statement. There is no such percentage disclosed in Brusilow 1993. Rather, Brusilow 1993 teaches that the drug is nearly completely conjugated with glutamine to form PAGN. *See* page 1337, right column.

Therefore, claims 1, 3, 6-8, 10, 30, 31, 33, 36-41, and 43 are not anticipated by Brusilow 1993. Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 102(b).

III. Claim Rejections Under 35 USC § 103

Claims 1-4, 6-8, 10, 11, 30-44 are rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over each of Brusilow 1991, Brusilow 1995, and Brusilow 1993 in view of ClinicalTrial.gov archi (NCT0055120, 2007) (hereinafter "ClinicalTrial.gov") and Brusilow (US

6,083,984 and US 5,968,979) (hereinafter "Brusilow '984 and '979"). Applicant respectfully traverses the rejection.

As discussed below, none of these references, either individually or collectively, provides teaching that discloses the claimed invention or would direct one skilled in the art to the claimed invention. Further, the invention represents a significant advance and is advantageous over the basis of dosing determinations disclosed in the art, which are being used even today.

a) The cited references do not teach or suggest determining dosage based on urinary PAGN

Applicant respectfully submits that it would not 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" as the Examiner states (page 8 of the Office Action) in view of the cited references because the method of determining dosage based on urinary PAGN was not taught by these references. As discussed above, Brusilow 1991, Brusilow 1995, and Brusilow 1993 do not teach determining a dosage of a PAA prodrug based on urinary PAGN. The references are completely silent on this point. To the contrary, if anything, the Brusilow references do not convey any recognition or need to take into account the conversion efficiency of the drug to determine dosage. Moreover, Clinical Trials, Brusilow '984, and Brusilow '979 do not add any teaching that would cure the deficiencies of Brusilow 1991, Brusilow 1995, and Brusilow 1993. As noted below, the adult dose of 20 grams/day of phenylbutyrate disclosed by Brusilow '979 (*see* column 2, line 15) and Brusilow '984 (*see* column 2, line 22) is the same as outlined in Brusilow 1991, which does not take into account conversion efficiency when determining dosage. As such, all the claimed elements were not provided in any of these references, whether taken singly or together.

Even further, Applicant respectfully submits that Brusilow 1991, Brusilow 1993 and Brusilow 1995 do not teach or suggest determining PAA prodrug dosage based on any output measurements, much less urinary PAGN as claimed. Rather, dosage was calculated based on dietary intake and an assumption about the amount of dietary intake excreted as waste nitrogen.

There was no disclosure indicating any output should be taken into account in determining dosage. Even more striking is that despite the fact that urinary PAGN was measured, none of Brusilow 1991, Brusilow 1993 and Brusilow 1995 make any suggestion to use urinary PAGN as a basis to determine dosing. Further, Applicant respectfully submits that ClinicalTrial.gov and Brusilow '984 and '979 cited by the Examiner as secondary references do not cure the deficiencies of the three primary references, all of which are discussed further below.

Brusilow 1991

In Brusilow 1991, as discussed above, drug dosage was pre-determined in the three studies performed. Specifically, a theoretical calculation was used to determine dosage based on results reported by Calloway and Margan "that on dietary nitrogen intakes (g/d) of 6.5-7.5 (40.6-46.9 g of protein/d) normal adult males excreted 3.16 ± 0.3 g/d of urea nitrogen, approximately 47% of their dietary nitrogen". *See* Brusilow 1991, page 147, right column. Based on this assumption that a subject would excrete 47% of dietary nitrogen, the amount of drug required to eliminate the expected amount of waste nitrogen excreted by a subject could then be calculated.

Moreover, Brusilow 1991 never suggested determining or adjusting dosages in any of the three clinical studies in view of the data observed including data of various output measurements. Specifically, Brusilow 1991 described measuring urinary levels of PAGN, nitrogen, urea and ammonium, as well as plasma levels of phenylacetate, phenylbutyrate, PAG, glutamine and ammonium to show that PAG may replace urea to eliminate waste nitrogen from the body. *See* Brusilow 1991, page 148, left column. Despite having measured these outputs, however, Brusilow 1991 concludes that "the appropriate dose will be a function of dietary nitrogen and nitrogen retention". *See* page 149, middle of right column.

Brusilow 1991 would not have led one skilled in the art to use urinary PAGN as a factor to be taken into account (*i.e.*, as a basis) to determine dosage. Instead, Brusilow 1991 uses a set dose based on other factors, and with respect to PAGN teaches that the drug is completely, or nearly so, conjugated with glutamine to form PAGN. *See* page 149, right column.

Brusilow 1993

In Brusilow 1993, as discussed above, drug dosages were pre-determined in the one study performed based on the assumptions made in Brusilow 1991. Brusilow 1993 also never suggested determining dosages in this study based on any other factor, even in view of the data observed. Specifically, Brusilow 1993 described measuring urinary levels of urea nitrogen, PAG, phenylacetate, phenylbutyrate and plasma levels of ammonium and glutamine to show the existence of a reciprocal relationship between urinary urea and PAGN such that waste nitrogen can exit either as PAGN or as urea. *See* Abstract. Moreover, urinary PAGN was not measured as a basis or factor to be taken into consideration to determine dosage.

Despite having measured these outputs, however, Brusilow 1993 never teaches or suggests determining dosages based on any of these measurements, much less urinary PAGN as claimed. Instead, and in significant contrast, Brusilow 1993 does not refer to any use of conversion efficiency as a basis for dosing.

Brusilow 1995

Brusilow 1995, as discussed above, is a review article based on the previous studies in Brusilow 1991 and 1993 and as such reiterates the teachings regarding dosage as discussed above. Brusilow 1995 teaches that "a 20 gram daily dose of sodium phenylbutyrate . . . is equivalent to the amount of urea nitrogen excreted by an adult receiving a very low protein diet". *See* page 305. In other words, Brusilow 1995 articulates the understanding that dosages were determined by calculating the amount of drug required to eliminate the expected amount of waste nitrogen excreted based on the subject's dietary intake without taking into account any conversion efficiency, let alone conversion efficiency as measured by urinary PAGN.

ClinicalTrial.gov

As the Examiner states, ClinicalTrial.gov describes a dose-escalation study of glyceryl tri (4-phenylbutyrate) (*i.e.*, GT4P) to treat urea cycle disorders in comparison to Buphenyl®. *See*

Brief summary on page 1. Dosing of Buphenyl® and GT4P in this study was pre-determined. Specifically, subjects were prescribed to take Buphenyl® TID (not to exceed 20 grams/day), and the GT4P dose was calculated to contain the same amount of phenylbutyrates as the subject's prescribed daily dose of Buphenyl®. *See* Intervention on page 2.

Moreover, ClinicalTrial.gov never suggested determining dosing in view of the variables measured as described in the reference. These variables were disclosed as being measured for a purpose other than as a basis for determining dosing. ClinicalTrial.gov described measuring various plasma and urinary metabolites to study pharmacokinetics and pharmacodynamics when the patient switched from Buphenyl® to GT4P and when the dose of GT4P was increased. *See* Secondary outcomes on page 2. Despite having measured various plasma and urinary metabolites, including urinary PAGN, ClinicalTrial.gov did not teach or even suggest determining Buphenyl® and/or GT4P dosages based on any of these measurements, much less urinary PAGN as claimed. In fact, Clinical Trial makes no mention of percentage conversion of PAA prodrug into urinary PAGN.

Brusilow '984 and '979

Brusilow '984 and '979 disclose new forms of prodrugs for phenylacetate to treat nitrogen retention disorders, as well as β-hemoglobinopathies, anemia and cancer. *See* Abstract of Brusilow '984 and '979.[1] Aside from a very general statement directed to dosing that points out that dosing can vary widely case to case, the only disclosure Brusilow '984 and '979 provides regarding dosing of sodium phenylbutyrate is that its daily dose is 20 grams/day. *See* Brusilow '984, column 2, lines 22-23; Brusilow '979, column 2, lines 14-15. Neither reference discloses or even suggests one should use urinary PAGN as a basis (or factor to be taken into account) for determining dosage, and the dose of 20 grams/day is in essence the same as proposed by Brusilow 1991 which does not take into account conversion efficiency when determining dosage.

Therefore, Applicant respectfully submits that none of the cited references, either individually or collectively, teaches or suggests determining PAA prodrug dosage based on urinary

[1] Applicant respectfully notes that Brusilow '984 was filed as a divisional application from Brusilow '979.

PAGN output. As discussed above, none of these disclosures makes any reference to using this measurement as a basis for dosage determination. When combined, this is still the case. On this basis alone, Applicant respectfully submits that this rejection may be withdrawn.

b) One of ordinary skill in the art would not have been motivated to determine dosage based on PAGN output

This point has been discussed above in discussing the lack of teaching in the cited references. Despite the fact that various outputs (including urinary PAGN) were measured, dosing at the time of the claimed invention was not determined based on urinary PAGN output, nor was any suggestion made in any of these references that this measurement should be used as a basis for determining dosing. Applicant respectfully submits that the fact that this parameter was measured and reported does not render the claimed invention obvious, especially in view of the fact that this parameter was measured for a different purpose, and despite reporting this measurement none of the references even indicated that this measurement should be used as a basis for determining dosage.

At the time of the claimed invention, one of skill in the art lacked motivation to modify the way in which dosing was previously determined because if anything the references taught that the prodrug was completely or nearly completely converted into PAGN output. *See e.g.*, Brusilow 1991, page 149, right column ("phenylbutyrate appears to be completely oxidized to phenylacetate and that phenylacetate is completely, or nearly so, conjugated with glutamine"). Based on this fundamental assumption, one of skill in the art would have assumed that dosing of the prodrug was driven by the amount of waste nitrogen present in the subject (based on dietary nitrogen and nitrogen retention).

Thus, Applicant respectfully submits that one of ordinary skill would not have been motivated to determine PAA prodrug dosages based on urinary PAGN output. Despite the fact urinary PAGN and other output variables were measured in these references, it would not have been obvious for one of skill in the art to change the dosing rationale based on the assumptions discussed above that were known at the time of the claimed invention.

c) Surpising aspects and advantages of the current invention

In contrast to the dominant and enduring teachings of the art, Applicant discovered that the fundamental predicate(s) of dosing presented by Brusilow et al. was incomplete and that dosing of the prodrug could be significantly more precisely determined if based not only on dietary intake and nitrogen retention but also taking into account utilization efficiency of the PAA prodrug. *See* Examples 2 and 3. In view of these findings, Applicant has discovered that dosing of the PAA prodrug can more precisely be determined by taking into account the levels of urinary PAGN output since the PAA prodrug is converted in PAGN before reaching the systemic circulation, rendering blood levels in comparison unreliable for determining dosing. This is particularly significant in the context of nitrogen retention disorders, including urea cycle disorders and hepatic encephalopathy, in which ammonia levels must be precisely controlled over decades.

The use of urinary PAGN as a basis to determine dosage of a PAA prodrug presents significant advantages over what was previously known in the art. The methods recited in the pending claims provide a more reliable method for determining PAA prodrug dosage compared to the theoretical dosage calculation described in Brusilow 1991. Specifically, measuring PAGN as the output provides a direct measure of how much ammonia the drug is mobilizing for elimination. Moreover, measuring the urinary levels of PAGN more accurately captures the prodrug's activity than blood levels since the prodrug can be metabolized before reaching the systemic circulation. This insight was previously not appreciated in the art at the time of the claimed invention, and was appreciated by Applicant when plasma and urinary metabolites were compared. In particular, the results in Example 3 of the application show that plasma metabolite levels did not correlate well with the dosage. *See* table in paragraph [00117] of the specification. It was surprisingly found that plasma PBA levels during dosing were directionally lower than those during treatment with sodium PBA, despite directionally better ammonia control. Thus, plasma metabolite did not correlate consistently with, and were in some cases opposite to, drug effect.

The methods recited in the pending claims also take into account patient variability based on the nitrogen retention disorder, the severity of the disorder, and the patient's urea synthetic

capacity by measuring the observed urinary excretion of PAGN. Thus, the method allows one of skill in the art to achieve more precise dosing for these patients suffering from a nitrogen retention disorder. Moreover, the use of a urinary output to determine dosage is a more practical and convenient approach compared repeated blood samples that require medical assistance.

In view of the entire record and the reasons stated above, claims 1-4, 6-8, 10, 11, 30-44 are not obvious based on the cited references. Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 103(a).

IV. Double Patenting

Claims 1-4, 6-8, 10, 11, 30-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-14 of copending Application No. 13061507. Applicant respectfully traverses the rejection. Applicant assumes that Examiner is referring to co-pending Application No. 13/061,509 (hereinafter "the '509 application"). To the extent the extent that a double patenting rejection in view of the '509 application applies to the pending claims, Applicant requests that it be held in abeyance pending disposition of any other rejections. Should the double patenting rejection remain the only pending rejection, Applicant requests that the rejection be withdrawn and this application, as the earlier-filed application, be allowed to issue in accordance with MPEP 804.I.B.1.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 643982000100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 21, 2011

Respectfully submitted,

E-Signature: /Catherine M. Polizzi/
Catherine M. Polizzi
Registration No.: 40,130
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5651

sf-3059217

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in the application:

Claim 1 (Previously Presented): A method to determine an effective dosage of a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof for a patient in need of treatment for a nitrogen retention disorder selected from urea cycle disorder and hepatic 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 the effective dosage of the prodrug to produce a desired ammonia scavenging effect.

Claim 2 (Original): The method of claim 1, wherein urinary PAGN output is determined as a ratio of the concentration of urinary PAGN to urinary creatinine.

Claim 3 (Currently Amended): The method of claim 1, wherein the method comprises calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into urinary PAGN of about 60% to about 75%.

Claim 4 (Previously Presented): The method of claim 1, wherein the prodrug is HPN-100, and wherein administering the effective dosage of HPN-100 to the patient produces a normal plasma ammonia level in the patient.

Claim 5 (Cancelled).

Claim 6 (Currently Amended): A method to determine a dosage of a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof for a patient having a nitrogen retention disorder selected

from urea cycle disorder and hepatic encephalopathy, which comprises measuring urinary excretion of phenylacetyl glutamine (PAGN) in a patient to whom the PAA prodrug has been administered and calculating the dosage of the PAA prodrug based on a utilization efficiency for the prodrug conversion into urinary PAGN of about 60% to about 75%.

Claim 7 (Previously Presented): The method of claim 6, wherein the dosage of the PAA prodrug is calculated from the patient's dietary protein intake.

Claim 8 (Previously Presented): The method of claim 7, wherein the dosage of the PAA prodrug is adjusted to account for the patient's residual urea synthesis capacity.

Claim 9 (Cancelled).

Claim 10 (Previously Presented): The method of claim 1, wherein the PAA prodrug is phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof.

Claim 11 (Previously Presented): The method of claim 1, wherein the PAA prodrug is HPN-100.

Claims 12-29 (Cancelled).

Claim 30 (Previously Presented): The method of claim 1, wherein the PAA prodrug is sodium phenylbutyrate.

Claim 31 (Previously Presented): The method of claim 1, wherein the nitrogen retention disorder is urea cycle disorder.

Claim 32 (Previously Presented): The method of claim 1, wherein the nitrogen retention disorder is hepatic encephalopathy.

Claim 33 (Previously Presented): The method of claim 6, wherein the nitrogen retention disorder is urea cycle disorder.

Claim 34 (Previously Presented): The method of claim 6, wherein the nitrogen retention disorder is hepatic encephalopathy.

Claim 35 (Previously Presented): The method of claim 6, wherein the prodrug is HPN-100.

Claim 36 (Previously Presented): The method of claim 6, wherein the prodrug is PBA or a pharmaceutically acceptable salt thereof.

Claim 37 (Previously Presented): The method of claim 6, wherein the prodrug is sodium phenylbutyrate.

Claim 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 thereof to a patient having a nitrogen retention disorder selected from urea cycle disorder and hepatic encephalopathy, the method comprising determining urinary phenylacetylglutamine (PAGN) excretion of the patient following administration of the PAA prodrug, determining a dose of the PAA prodrug based on the urinary PAGN excretion, and administering the dose to the patient.

Claim 39 (Currently Amended): The method of claim 38, wherein the dosage of the PAA prodrug is based on a utilization efficiency for the PAA prodrug conversion into urinary PAGN of about 60% to about 75%.

Claim 40 (Previously Presented): The method of claim 38, wherein PBA or a pharmaceutically acceptable salt thereof is administered.

Claim 41 (Previously Presented): The method of claim 38, wherein sodium phenylbutyrate is administered.

Claim 42 (Previously Presented): The method of claim 38, wherein HPN-100 is administered.

Claim 43 (Previously Presented): The method of claim 38, wherein the disorder is urea cycle disorder.

Claim 44 (Previously Presented): The method of claim 38, wherein the disorder is hepatic encephalopathy.

Claim 45 (New): The method of claim 1, wherein the prodrug is sodium phenylbutyrate, and wherein administering the effective dosage of the sodium phenylbutyrate to the patient produces a normal plasma ammonia level in the patient.

Electronic Acknowledgement Receipt

EFS ID:	11238729
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:	25225
Filer:	Catherine M. Polizzi/Farah O'Sullivan
Filer Authorized By:	Catherine M. Polizzi
Attorney Docket Number:	643982000100
Receipt Date:	21-OCT-2011
Filing Date:	07-JAN-2009
Time Stamp:	14:39:10
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	Miscellaneous Incoming Letter	64398-20001_00__Transmittal-OAR.pdf	23892 d9fa6077b2515e5f4c9ba1e6b8707fd01c4a8f84	no	1

Warnings:	
Information:	

2		64398-2000100_Response_to_OA.pdf	76357 eb128d20a0ed0983e7809e4a8c6777012ad108c4	yes	18

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Abstract	6	18

Warnings:	
Information:	
Total Files Size (in bytes):	100249

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

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

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

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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	10/21/2011	(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 $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***12	= 0	X $ =		OR	X $250=	0
	☐ 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	0

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:
/ANDREA FREEMAN/

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

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

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	19

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

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply (18 pages)
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP (Customer No. 25225)		
Signature	/Catherine M. Polizzi/		
Printed name	Catherine M. Polizzi		
Date	October 21, 2011	Reg. No.	40,130

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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

25225 7590 11/18/2011

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

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

NOTIFICATION DATE	DELIVERY MODE
11/18/2011	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):

EOfficeSD@mofo.com
PatentDocket@mofo.com
Drcaldwell@mofo.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) *Catherine Polizzi*.

(3) *Bruce Scharschmidt*.

(4) *Anita Choi*.

Date of Interview: *14 October 2011*.

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: *1,2,6 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...)

Applicant summarized the invention and discussed that while the art discloses measuring PAGN output, that applicant believe that the art does not suggest determining an effective dosage in respone to measured PAGN output. Applicant argued the art asssumes complete conversion of the drug. Applicant disclosed that blood levels are unpredictable and that urinary measurements are more accurate. Applciant argues that the art teaches that all you need to know is the initial dose. Applicant argued that no one has suggested individualizing care as each patients output is different. The examiner suggested that the art suggested PAGN output as a function of dose and that the invention appears to be a simple pharmacokinetic study. No agreement was reached in regards to patentability. .

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

/Tiffany M Gough/ 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.

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 *21 October 2011*.

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) *1-4,6-8,10,11 and 30-45* 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) *1-4,6-8,10,11 and 30-45* 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 _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *11/9/2011* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 10/21/11 has been received and entered into the case. Claims *1-4, 6-8, 10, 11, 30-45* are pending and have been considered on the merits. All arguments and amendments have been considered.

Claim Rejections - 35 USC § 102

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

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

Claims 1, 3, 10, 30, 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Brusilow (Ped. Res., 1991).

Applicant claims a method to determine an effective dosage of a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof for a patient in need of treatment for a nitrogen retention disorder selected from urea cycle disorder and hepatic 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. The method comprises calculating the dosage of prodrug based on utilization efficiency for prodrug conversion into PAGN of about 60% to about 75%. The method comprises wherein the dosage of the PAA prodrug is calculated from the patient's dietary protein intake and the dosage of the PAA prodrug is adjusted to account for the patient's residual urea synthesis capacity. The method also claims the PAA prodrug is sodium phenylbutyrate. and the nitrogen retention disorder is urea cycle disorder.

Brusilow 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 60% to about 75% 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 (results section, p. 148, whole page). 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.

Thus, the reference anticipates the claimed subject matter.

Claims 1, 10, 30, 31, 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Brusilow (1995).

Brusilow 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 (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).

Thus, the reference anticipates the claimed subject matter.

Claims 1, 10, 30, 31, 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Brusilow et al. (Metabolism, 1993).

Brusilow 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).

Thus, the reference anticipates the claimed subject matter.

Response to Arguments

Applicant's arguments filed 10/21/2011 have been fully considered but they are not persuasive. Applicant argues that Brusilow 91 does not teach calculating the prodrug dosage or the conversion of 60-75% of the drug.

It is the Examiners position that Brusilow does teach the claimed invention of claim 1. Applicant claims determining the patients urinary PAGN output and determining from said output the effective dosage to produce a desired effect. Brusilow teach administering the claimed prodrug and measuring urinary PAGN output. Brusilow determines which dosage was capable of producing the desired effect. Brusilow also teach an 80-90% utilization efficiency for prodrug conversion (Results section, p. 148). Brusilow also compare the predicted and measured PAGN output after administration of the prodrug. From Brusilow's study, one of ordinary skill in the art can determine the effective dosage to produce a desired effect. Brusilow states that PAGN synthesis is a function of the dose of phenylacetate or phenylbutyrate. Brusilow anticipates the claimed invention.

In response to Brusilow '95 and '93, applicant argues the dose is not calculated based upon PAGN output.

The same arguments regarding Brusilow '91 apply. Brusilow teach administering the claimed prodrug and measuring urinary PAGN output. Brusilow determines the effective dosage based upon PAGN output, which was capable of producing the desired effect. Further Brusilow '83 teach 92% conversion (p.1337, Results section).

Thus, it is the Examiners position that Brusilow teach administering a prodrug to a patient in need thereof and measuring PAGN output to determine the effective dosage to produce a desired effect. Further, the art teaches a range of prodrug conversion based upon PAGN output and even recognize that PAGN synthesis is a function of the dose of phenylacetate or phenylbutyrate.

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 1-4, 6-8, 10, 11, 30-45 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) and Brusilow (US6083984, US5968979)..

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 a utilization efficiency for prodrug conversion into PAGN of about 60% to about 75% 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).

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).

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 dislosed by Brusilow. 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.

It is the Examiners position that 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. It is the Examiners position that the art of record clearly suggest the dose to be a result effective variable regarding PAGN output. Further, the clinical trials document teach 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.

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 10/21/2011 have been fully considered but they are not persuasive.

Applicant argues that the art does not teach calculating dosage based upon PAGN output. Applicant argues that the dose was predetermined in the Brusilow studies. Applicant argues that the clinical trials reference does not suggest dosing based upon variables measured, i.e. urinary PAGN and that they do not suggest percent conversions of prodrug into PAGN.

It is the Examiners position that 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. It is the Examiners position that the art of record clearly suggest the dose to be a result effective variable regarding PAGN output. Further, the clinical trials document teach 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.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-8, 10, 11, 30-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 13061507. Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are drawn to the methods of determining an effective dose of a PAA prodrug. Claim 1 of the instant invention is drawn to both PBA or HPN-100, while '507 is drawn to HPN-100 or a PAA prodrug which is either HPN-100 or PBA, for example, claims 1, 9-11.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant wishes to hold the above rejection in abeyance until allowable subject matter is indicated.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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

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

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	tmg
Google	7/13/2011updated 11/9/11	tmg
eDAN inventor search	7/13/2011	

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

/TIFFANY GOUGH/ Examiner.Art Unit 1651	

Electronic Acknowledgement Receipt

EFS ID:	11765631
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:	25225
Filer:	Catherine M. Polizzi/Lindsay Seydel
Filer Authorized By:	Catherine M. Polizzi
Attorney Docket Number:	643982000100
Receipt Date:	05-JAN-2012
Filing Date:	07-JAN-2009
Time Stamp:	13:46:34
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	Petition automatically granted by EFS	petition-request.pdf	34812 85b31c479a5c416ad217c0da5bba7002641c3afd	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	34812

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Decision Date : January 5, 2012

In re Application of :

Bruce SCHARSCHMIDT

Application No : 12350111

Filed : 07-Jan-2009

Attorney Docket No : 643982000100

DECISION ON REQUEST TO WITHDRAW AS ATTORNEY/AGENTOF RECORD

This is an electronic decision on the Request to Withdraw as attorney or agent of record under 37 CFR § 1.36(b), filed January 5, 2012

The request is **APPROVED.**

The request was signed by Catherine Polizzi (registration no. 40130) on behalf of all attorneys/agents associated with Customer Number 25225 . All attorneys/agents associated with Cusotmer Number 25225 have been withdrawn.

Since there are no remaining attorneys of record, all future communications from the Office will be directed to the first named inventor or assignee that has properly made itself of record pursuant to 37 CFR 3.71, with correspondence address:

Name	UCYCLD Pharma, Inc.
Name2	
Address 1	7720 North Dobson Road
Address 2	
City	Scottsdale
State	AZ
Postal Code	85256
Country	US

As a reminder, requester is required to inform the first named inventor or assignee that has properly made itself of record pursuant to 37 CFR 3.71 of the electronically processed petition.

Telephone inquiries concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

Office of Petitions

Doc Code: PET.AUTO **Document Description: Petition automatically granted by EFS-Web**	PTO/SB/83 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**REQUEST FOR WITHDRAWAL AS ATTORNEY OR AGENT AND CHANGE OF CORRESPONDENCE ADDRESS**
Application Number	12350111
Filing Date	07-Jan-2009
First Named Inventor	Bruce SCHARSCHMIDT
Art Unit	1651
Examiner Name	TIFFANY GOUGH
Attorney Docket Number	643982000100
Title	METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

◉ Please withdraw me as attorney or agent for the above identified patent application and the practitioners of record associated with Customer Number: 25225

The reason(s) for this request are those described in 37 CFR:

10.40(b)(4)

Certifications

☒ I/We have given reasonable notice to the client, prior to the expiration of the response period, that the practitioner(s) intend to withdraw from employment

☒ I/We have delivered to the client or a duly authorized representative of the client all papers and property (including funds) to which the client is entitled

☒ I/We have notified the client of any responses that may be due and the time frame within which the client must respond

Change the correspondence address and direct all future correspondence to the first named inventor or assignee that has properly made itself of record pursuant to 37 CFR 3.71:

Name	UCYCLD Pharma, Inc.
Address	7720 North Dobson Road
City	Scottsdale
State	AZ
Postal Code	85256
Country	US

I am authorized to sign on behalf of myself and all withdrawing practitioners.	
Signature	/Catherine Polizzi/
Name	Catherine Polizzi
Registration Number	40130

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/350,111	01/07/2009	Bruce SCHARSCHMIDT	643982000100

CONFIRMATION NO. 6290

POWER OF ATTORNEY NOTICE

25225
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

OC000000051843888

Date Mailed: 01/06/2012

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/05/2012.

- The withdrawal as attorney in this application has been accepted. Future correspondence will be mailed to the new address of record. 37 CFR 1.33.

/eefswuser/

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

Electronic Acknowledgement Receipt

EFS ID:	11821450
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
Correspondence Address:	UCYCLD Pharma, Inc. - 7720 North Dobson Road - Scottsdale AZ 85256 US - -
Filer:	Patrick D. Morris/Colleen Kirchner
Filer Authorized By:	Patrick D. Morris
Attorney Docket Number:	643982000100
Receipt Date:	12-JAN-2012
Filing Date:	07-JAN-2009
Time Stamp:	14:22:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	8001US01_POA.pdf	508317 c421042128b637f151af9234e0b3470ecd9ed097	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	508317		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/81 (01-09)
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POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	12/350,111
Filing Date	January 7, 2009
First Named Inventor	Bruce Scharschmidt
Title	Methods of Treatment Using Ammonia-Scavengi
Art Unit	1651
Examiner Name	Tiffany Maureen Gough
Attorney Docket Number	

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

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I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on October 27, 2010

SIGNATURE of Applicant or Assignee of Record

Signature	Len Smith	Date	1-11-2012
Name	Len Smith	Telephone	
Title and Company	Principal Planner, Ucyclyd Pharma, Inc.		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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.
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/350,111	01/07/2009	Bruce SCHARSCHMIDT	643982000100

CONFIRMATION NO. 6290

POA ACCEPTANCE LETTER

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

OC000000052102466

Date Mailed: 01/24/2012

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/12/2012.

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

/atesfai/

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

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

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. I am currently Senior Vice President and Chief Medical Officer at Hyperion Therapeutics, a privately-held biopharmaceutical company. Prior to joining Hyperion in 2008, I held Vice President positions at Novartis Vaccines & Diagnostics (2006-08) and Chiron Corporation (1996-2006), where I was Corporate Vice President and headed the department responsible for design and execution of clinical trials of investigational vaccines and therapeutics. Prior to joining Chiron, I was Chief of Gastroenterology and Professor of Medicine at the University of California, San Francisco and an NIH-funded investigator for nearly two decades (1977-1996). I have authored approximately 200 research and review articles, mostly in the field of liver disease, and I served as Associate Editor of Gastroenterology (1981-86), Editor-in-Chief of the Journal of Clinical Investigation (1987-92), and President of the American Society for Clinical Investigation (1992-93).

2. HPN-100 is a phenylacetic acid (PAA) prodrug that acts as an ammonia scavenger. HPN-100 is currently being developed for the treatment of urea cycle disorders (UCDs) and hepatic encephalopathy (HE), a neuropsychiatric disorder which can develop as a complication of advanced liver disease. Since April 2008, my responsibilities at Hyperion have included the design and execution of clinical trials directed to obtaining regulatory approval for HPN-100. Data from these trials forms the basis of above-captioned US Patent Application No. 12/350,111 ("'111 Application"), of which I am the inventor.

3. Clinical trial data forming the basis of and/or validating the findings set forth in the '111 Application includes data from healthy adults (McGuire et al. 2010. *Pharmacology and safety of glycerol phenylbutyrate in healthy adults and adults with cirrhosis*. Hepatology 51:2077), patients with cirrhosis (McGuire 2010; Ghabril et al. *Glycerol phenylbutyrate (GPB) administration in patients with cirrhosis and episodic hepatic encephalopathy (HE)*. Accepted for presentation at Digestive Disease Week, 2012), and UCD patients (Lee et al. 2010. *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; Lichter-Konecki et al. 2011. *Ammonia (NH3) control in children with urea cycle disorders (UCDs); phase 2 comparison of sodium phenylbutyrate and glycerol phenylbutyrate*. Mol Genet Metab 103:323; Diaz et al. 2011. *Phase 3 blinded, randomized crossover comparison of sodium phenylbutyrate (NaPBA) and glycerol phenylbutyrate (GPB): Ammonia (NH3) control in adults with urea cycles disorders (UCDs)*. Mol Genet Metab 102:276 (Society for Inherited Metabolic Disease (SMID) Abstract)). I am a co-author on each of these cited publications, copies of which are included herewith.

4. HPN-100 clinical trials enrolling UCD patients involved 24 hour blood sampling and urine collections during steady state dosing (i.e., following 7-14 days of continuous dosing) with either sodium phenylbutyrate (NaPBA, another nitrogen scavenging PAA prodrug) or HPN-100. The studies reported in the Lee 2010 and Lichter-Konecki 2011 publications were fixed sequence NaPBA to HPN-100 switchover studies, whereas the study reported by Diaz 2011 was a randomized, active controlled, double blind, crossover study.

5. The amended independent claims submitted herewith for the '111 Application are directed to methods of determining an effective initial dosage of a PAA prodrug (claim 1), methods of treating a patient having a nitrogen retention disorder using a PAA prodrug (claim 6), and methods of administering a PAA prodrug (claim 38). Each of these claims contains a limitation specifying that the mean conversion of PAA prodrug to urinary PAGN is 60 to 75%. This percent conversion is derived from the clinical study data discussed above, including the only study in pediatric UCD patients (Lichter-Konecki 2011), the largest adult UCD study (Diaz 2011), and a study that included cirrhotics with decompensated cirrhosis (Ghabril 2012). As summarized in Table 1, these studies revealed a mean percentage conversion of PAA prodrug to PAGN of 60-75%.

Table 1: Recovery of orally administered PBA as urinary PAGN

	Percent conversion of PBA to urinary PAGN Mean (SD)	
Study population (# of patients) (citation)	HPN-100	NaPBA
Adult UCD subjects ages ≥18 yrs (N = 44) (Diaz 2011)	70.9 (18.9)	71.4 (19.6)
Pediatric UCD subjects ages 6-17 yrs (N = 11) (Lichter-Konecki 2011)	66.4 (24.9)	69 (23.9)
Adults with advanced cirrhosis 6 mL BID (N = 14) 9 mL BID (N = 7) (Ghabril 2012)*	 59.1 (19) 72.7 (8.7)	 Not done Not done

* Derived from data presented in abstract; manuscript in preparation

6. UCDs result from abnormalities in genes encoding for one of six enzymes or two mitochondrial transporters necessary for the normal function of the urea cycle. Each of these genes exhibits multiple mutations corresponding to different phenotypes, and each UCD patient is therefore genetically unique. Dosing needs to be precisely titrated for each patient such that they receive sufficient PAA prodrug to allow excretion of waste nitrogen they are unable to excrete as urea (to avoid hypammonemia), but not so much drug that they are at risk for drug toxicity.

7. PAA prodrug dosing is currently imprecise and based on clinical judgment, measurement of blood ammonia (which varies widely over the course of the day even in well controlled patients; see, e.g., Lee 2010, Lichter-Konecki 2011), and theoretical calculations that assume complete or nearly complete conversion of PBA to urinary PAGN (see, e.g., Brusilow. 1991. *Phenylacetylglutamine may replace urea as a vehicle for waste nitrogen excretion*. Pediatr Res 29:147; Brusilow & Finkelstein. 1993. *Restoration of nitrogen homeostasis in a man with ornithine transcarbamylase deficiency*. Metabolism 42:1336).

8. As disclosed in the '111 Application and recited in the presently amended claims, the mean conversion of PAA prodrugs to urinary PAGN is 60 to 75%. This conversion percentage is significantly less than previously reported by Brusilow. Since the clinical effect of PAA prodrugs is mediated by PAGN excretion, the conversion rate disclosed by Brusilow exposes patients to a risk of underdosing. The difference between 60% conversion and 90% conversion, for example, represents a 50% difference in drug effect,

which is clinically very important and might mean the difference between normal mental function and significant and often permanent impairment. The disclosure of a mean conversion of PBA to urinary PAGN of 60-75% will allow for improved dosing of UCD and HE patients, resulting in better clinical efficacy and decreased likelihood of negative side effects.

9. 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: Feb 21 2012

Bruce F Scharschmidt

Dr. Bruce Scharschmidt

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.

REMARKS

Interview

Applicant wishes to thank the Examiner for the in-person interview held on February 16, 2012. During the interview, Applicant and Examiner discussed distinctions between the present application and the cited Brusilow references, as well as possible claim amendments. The amended claim set provided herein reflects these discussions.

Independent claim amendments

Claim 1 has been amended to specifically recite the use of the mean conversion of PAA prodrug to PAGN of 60-75% to determine an effective initial dosage of a PAA prodrug for a subject with a nitrogen retention disorder. Claim 6 as amended is similar to claim 1 in that it recites steps for determining an effective initial dosage of a PAA prodrug for a subject with a nitrogen retention disorder. Claim 6 differs from claim1 in that it is framed as a method of treatment, and therefore includes the additional step of administering the PAA prodrug. Claim 38 has been amended to specify that determination of an effective dosage of PAA prodrug is based on a mean conversion of PAA prodrug to PAGN of 60-75%.

All of the amended claims contain a limitation regarding 60-75% mean conversion of PAA prodrug to PAGN. The insertion of this limitation into all of the present claims is made solely to advance prosecution of the present case, and is done without prejudice to pursuing broader claims directed to evaluation of PAA prodrug dosage using urinary PAGN measurements generally in one or more continuing applications.

Application disclosure

The present application discloses several novel findings regarding the relationship between PAA prodrug administration and urinary PAGN output. Among these is the 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 more detail below, this finding is contradictory to the knowledge in the art at the time the present application was filed, which disclosed that PAA was nearly completely converted to urinary PAGN (with a percent conversion of 80% or greater). Applicant has submitted

herewith the declaration of inventor Bruce Scharschmidt, which provides additional details about the clinical trials that led to a more accurate identification of the percent conversion of PAA to PAGN. This declaration also discusses the impact that relatively small variations in PAA prodrug dosage can have on efficacy and patient health, thereby underscoring the importance of the difference in PAA to urinary PAGN conversion percentage disclosed in the present application versus the prior art.

Anticipation

Anticipation rejection 1

The Office Action rejects independent claim 1 and dependent claims 3, 10, 30, and 31 as anticipated by Brusilow Pediatr Res 29:147 (1991) ("Brusilow 1991").

According to the Office Action, Brusilow 1991 "teaches 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, 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)." The Office Action goes on to assert that Brusilow 1991 "teaches calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into PAGN of about 60% to about 75% and calculating the dosage of the prodrug based on multiple factors including the patient's dietary protein intake and the patient's residual urea synthesis capacity (results section, p. 148, whole page)." Finally, the Office Action asserts that Brusilow 1991 "determine an effective dosage of sodium phenylbutyrate for treating and maintaining UCD's based on PAGN conversion."

Response

Applicant has canceled claims 3 and 10, rendering the rejection moot with regard to those claims.

Prior to Brusilow 1991, it was known that sodium PAA and other PAA prodrugs were converted to PAGN following patient administration, and that PAGN was excreted in the urine, resulting in the removal of waste nitrogen. As such, PAA prodrugs were frequently administered to patients with urea synthesis disorders to increase waste nitrogen removal. Although it was known that PAGN could serve as a partial substitute for urea in the removal of waste nitrogen, the degree to which it could substitute for urea had not been studied (Brusilow 1991, p. 147, paragraph spanning left and right columns).

The premise of Brusilow 1991 is that PAGN (referred to therein as "PAG") can fully replace urea as a vehicle for waste nitrogen excretion when PBA or PAA is administered at sufficient dosage (Brusilow 1991, p. 147, right column, 1st full paragraph). Based on a previous reference that had shown approximately 47% of dietary nitrogen (3.16 g excreted per 6.5-7.5 g ingested) is excreted as urea in normal adult males, Brusilow 1991 estimated that "*[a]ssuming complete conversion* to its amino acid conjugate, the oral administration of 18 g of sodium phenylacetate should result in excretion of 3.23 g of PAG nitrogen" (Brusilow 1991, p. 147, right column, 4th full paragraph). Similarly, based on a previous study showing approximately 47% of dietary nitrogen (0.094 g excreted per 0.2 g ingested) excreted as urea in children on a protein-restricted diet, Brusilow 1991 estimated that "[t]o excrete 0.094 g/kg/d of PAG nitrogen would require 0.524 g/kg/d of sodium phenylacetate" (Brusilow 1991, p. 147, right column, 5th full paragraph). This calculation again assumes complete conversion of sodium PAA to PAGN.

Brusilow 1991 evaluated the relationship between sodium PAA administration and urinary PAGN excretion in a single child with carbamyl phosphate synthetase deficiency (Brusilow 1991, paragraph spanning pp. 147 and 148). The results of this study are set forth in Tables 1 and 2 (p. 148). Table 1 shows "the stoichiometry between phenylacetate or phenylbutyrate administration and urinary excretion of PAG" (Brusilow 1991, p. 148, right column, 3rd full paragraph). As shown in Table 1, 83, 90, and 80% of the predicted amount of PAGN was actually measured in urine at periods I, II, and III, respectively (Table 1, 4th row). Brusilow 1991 summarized these results by stating that "[t]he amount of PAG excreted was a function of phenylacetate or phenylbutyrate dose; between 80 and 90% of the predicted

amount of PAG synthesized is excreted" (Brusilow 1991, p. 148, right column, 3rd full paragraph). Elsewhere, Brusilow 1991 states "[e]xamination of the stoichiometry between sodium phenylacetetate or phenylbutyrate administration and the excretion of PAG as shown in Table 1 demonstrates both that phenylbutyrate appears to be completely oxidized to phenylacetate and that phenylacetate is completely, or nearly so, conjugated with glutamine" (Brusilow 1991, p. 149, paragraph spanning left and right columns), and "[t]hat complete conjugate of the drugs occurs may be further adduced by the insignificant amount of unchanged drugs or their esters in urine and by the lack of accumulation in overnight fasting plasma" (Brusilow 1991, p. 149, right column, 1st full paragraph). Overall, Brusilow 1991 concluded that "high doses of phenylacetate or phenylbutyrate will result in the synthesis and excretion of PAG nitrogen similar to the amount of urea nitrogen that is excreted in normal subjects on a low-protein diet" (Brusilow 1991, p. 149, right column, 5th full paragraph).

Contrary to the assertion in the Office Action, Brusilow 1991 does not teach a method for determining an effective dosage of a PAA prodrug by monitoring urinary PAGN output. The purpose of measuring urinary PAGN output in Brusilow 1991 was solely to determine whether PAGN could fully replace urea in removing waste nitrogen. Brusilow 1991 does not teach or suggest that urinary PAGN levels can be used as a means of evaluating PAA prodrug dosage. Further, there is no support for the Office Action's assertion that Brusilow 1991 "teaches calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into PAGN of about 60% to about 75%." As stated above, Brusilow suggests that PAA to PAGN conversion is complete or nearly complete, and discloses experimental results for a single patient showing a conversion of 80-90%.

Amended claims 1, 30, and 31 all recite a mean conversion of PAA prodrug to urinary PAGN of 60-75%. Since Brusilow 1991 does not teach or suggest this conversion percentage, the reference does not anticipate all of the elements of claims 30 and 31.

Anticipation rejection 2

The Office Action rejects independent claim 1 and dependent claims 10, 30, 31, and 45 as anticipated by Brusilow Metabolism 42:1336 (1993) ("Brusilow 1993"). Note that this anticipation rejection and the following anticipation rejection (based on Brusilow 1995) are

taken out of order in this response so that the Brusilow references may be addressed in chronological order.

According to the Office Action, Brusilow 1993 "teaches 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, 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)." The Office Action goes on to assert that Brusilow 1993 "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)." Finally, the Office Action asserts that Brusilow 1993 "determine an effective dosage of sodium phenylbutyrate for treating and maintaining UCD's based on PAGN conversion (discussion section)."

Response

Applicant has canceled claim 10, rendering the rejection moot with regard to this claim.

Brusilow 1993 evaluated the hypothesis that sodium PBA-induced PAGN biosynthesis in a subject with partial ornithine transcarbamylase (OTC) deficiency not only provides an additional vehicle for waste nitrogen excretion, but also suppresses residual urea nitrogen synthesis (Brusilow 1993, Abstract and p. 1336, right column, 1st full paragraph). Brusilow 1993 evaluated urinary PAGN, urea nitrogen, PAA, and PBA levels in a single 38 year old male with partial OTC deficiency both before (period I) and after (periods II and III) sodium PBA administration (Brusilow 1993, p. 1337, left column, 2nd and 3rd full paragraphs). During the PBA administration periods, the subject "excreted 487 mmols of

phenylacetylglutamine N, 92% of the theoretical amount if the entire 532 mmol sodium phenylbutyrate administered over the 6 days was conjugated with glutamine and excreted" (Brusilow 1993, p. 1337, right column, 4th full paragraph). Brusilow confirms this 92% figure elsewhere, stating "[o]f the 532 mmol (99 g) sodium phenylbutyrate administered over 6 days, 487 mmol (92%) was recovered in the urine as phenylacetylglutamine" (Brusilow 1993, p. 1338, right column, 1st full paragraph). Overall, Brusilow 1993 concluded that "phenylacetylglutamine synthesis provides an additional vehicle for waste N synthesis and suppresses urea N synthesis" (Brusilow 1993, p. 1338, left column, 2nd full paragraph).

Claims 1, 30, 31, and 45 all recite a mean conversion of PAA prodrug to urinary PAGN of 60-75%. As noted by the Office Action, Brusilow 1993 discloses a conversion percentage of 92%. Since Brusilow does not teach or suggest a 60-75% conversion of PAA prodrug to urinary PAGN, the reference does not anticipate all of the elements of claims 1, 30, 31, and 45.

Anticipation rejection 3

The Office Action rejects independent claim 1 and dependent claims 10, 30, 31, and 45 as anticipated by Brusilow Progress In Liver Diseases, Ch. 12 (1995) ("Brusilow 1995").

According to the Office Action, Brusilow 1995 "teaches 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, 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)." The Office Action goes on to assert that Brusilow 1995 "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 (p. 305)" and "determine an effective dosage of sodium phenylbutyrate for treating and maintaining UCD's and encephalopathy based on PAGN conversion (p. 303-306)."

Response

Applicant has canceled claim 10, rendering the rejection moot with regard to this claim.

Brusilow 1995 is a book chapter and does not present any new research findings. Instead, Brusilow 1995 serves as a review of the art relating to urea cycle disorders and the removal of waste nitrogen. In asserting that Brusilow 1995 teaches "a method to determine an effective dosage of a phenylacetic acid (PAA) prodrug," the Office Action cites pages 293, 300, and 302-306. However, the Office Action does not pinpoint where within these pages its conclusions are allegedly supported.

Cited pages 293 and 300 offer no support for the conclusions set forth in the Office Action. Page 293 of Brusilow 1995 includes three introductory paragraphs on urea cycle disorders and the first paragraph of a case study. The introductory paragraphs state, among other things, that hyperammonemia is a primary cause of clinical symptoms associated with urea cycle disorders (Brusilow 1995, p. 293, 1st full paragraph), and that one of the primary management problems for patients with such disorders is "prevention of nitrogen accumulation" (Brusilow 1995, p. 293, 3rd full paragraph). These introductory paragraphs do not, however, mention PAA, PBA, PAGN, or dose determination. Similarly, the first paragraph of the case study on page 293 describes the clinical presentation of a 26 year old female patient ((Brusilow 1995, p. 293, 4th full paragraph)), but is silent with regard to PAA, PBA, PAGN, or dose determination. Page 300 of Brusilow 1995 discusses the clinical presentation and symptoms associated with various late onset urea cycle disorders. In doing so, Brusilow 1995 states that increasing symptom severity is associated with increasing levels of plasma ammonium and glutamine (Brusilow 1995, p. 300, 3rd full paragraph). However, as with page 293, there is no mention of PAA, PBA, PAGN, or dose determination.

Pages 302 to 306 of Brusilow 1995 contain a section entitled "Treatment of urea cycle disorders." This section discusses alternate pathways for elimination of waste nitrogen, and the activation of these pathways to treat patients who have had one or more episodes of hyperammonemic encephalopathy (Brusilow 1995, p. 302, 3rd full paragraph). This section largely reiterates the disclosure of Brusilow 1991 and Brusilow 1993. At page 303, Brusilow

1995 notes that PBA administration activates the synthesis and excretion of PAGN, which in turn decreases urea synthesis (Brusilow 1995, p. 303, 1st full paragraph). Figures 12-6 and 12-7 show the pathway whereby PAA is conjugated with glutamine to form PAGN. Figure 12-8 shows the effect of PAA/PBA dosing on plasma levels of various compounds, including PAGN, but does not mention urinary excretion of PAGN or provide any detail regarding the relationship between PAA/PBA administration and PAGN levels other than to show that PAGN levels increase. Brusilow 1995 goes on to state that sodium PBA is administered to subjects with deficiencies of CPS, OTC, and ASD, and that "a 20 gram daily dose of sodium phenylbutyrate would activate the synthesis and excretion of approximately 3 grams of phenylacetylglutamine nitrogen" (Brusilow 1995, paragraph spanning pp. 303 and 305). This ratio of PBA administered to PAGN excreted represents approximately 100% conversion of PBA to PAGN, which matches the results disclosed in Brusilow 1991 and Brusilow 1993 (see above). Finally, Brusilow 1995 summarizes the findings of Brusilow 1993 (Brusilow 1995, p. 305, 1st full paragraph).

Claims 1, 30, 31, and 45 all recite a mean conversion of PAA prodrug to urinary PAGN of 60-75%. Like Brusilow 1991 and Brusilow 1993, Brusilow 1995 discloses nearly complete conversion of PAA prodrug to urinary PAGN (approximately 90%). Since Brusilow 1995 does not teach or suggest a 60-75% conversion of PAA prodrug to urinary PAGN, the reference does not anticipate all of the elements of claims 1, 30, 31, and 45.

Obviousness

Rejection

The Office Action rejects independent claims 1, 6, and 38 and dependent claims 2-4, 7, 8, 10, 11, 30-37, and 39-45 as obvious over Brusilow 1991, Brusilow 1995, and Brusilow 1993 in view of ClinicalTrials.gov NCT0055120 (2007) and Brusilow US Patent Nos. 6,083,984 and 5,968,979. According to the Office Action, "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." The Office Action goes on to assert that "Brusilow teaches calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into PAGN of about 60% to about 75% 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 (results section, p. 148, whole page)." Finally, the Office Action asserts that Brusilow 1991 "determine an effective dosage of sodium phenylbutyrate for treating and maintaining UCD's based on PAGN conversion."

Response

Applicant has canceled claims 3, 10, 36, and 40, rendering the rejection moot with regard to those claims.

As discussed above with regard to anticipation, there is no support for the Office Action's assertion that any of the Brusilow references teach "calculating the dosage of prodrug based on a utilization efficiency for prodrug conversion into PAGN of about 60% to about 75%." Notably, the Office Action does not cite any support for this conclusion. Brusilow 1991, 1993, and 1995 each disclose near complete conversion of PAA prodrug to PAGN, with specific conversion rates of 80-92%.

In responding to Applicant's previous arguments, the Office Action states that "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 1991)." The cited portion of Brusilow 1991 does state that "PAG nitrogen synthesis is a function of the dose of phenylacetate or phenylbutyrate." However, as shown in the present application, Brusilow 1991 got this "function" incorrect; PAA prodrugs are converted to PAGN at a rate of 60-75%, not 80-92% as taught by Brusilow 91.

The rejected claims all recite a mean conversion of PAA prodrug to urinary PAGN of 60-75%. None of the cited references teach or suggest this conversion percentage. As noted in the attached Scharschmidt declaration, small differences in PAA prodrug dosage can have

large effects on drug efficacy and patient health. Therefore, the difference in the percent conversion taught in the prior art and that recited in the present claims is significant. As such, Applicant asserts that the rejected claims are non-obvious over the combined references.

Double patenting

Rejection

The Office Action rejects independent claims 1, 6, and 38 and dependent claims 2-4, 7, 8, 10, 11, 30-37, and 39-44 on the grounds of nonstatutory obviousness-type double patenting over claims 1-14 of copending US Patent Appl. No. 13/061,507. This application appears to be a typographical error; Applicant assumes that the rejection is meant to refer to US Patent Appl. No. 13/061,509, entitled "Dosing and monitoring patients on nitrogen-scavenging drugs."

Concurrently with the present response, Applicant has filed an express Notice of Abandonment for the '509 Application. Applicant asserts that abandonment of the '509 Application renders the double patenting rejection moot.

CONCLUSION

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

Respectfully submitted,

Perkins Coie LLP

Date: February 21, 2012

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AMENDMENTS TO THE CLAIMS

The following complete listing of claims replaces all previous claims in the application. Applicant has amended claims 1, 2, 4, 6, 7, 8, 30, 37, 38, 39, 41, 42, and 45, and canceled claims 3, 10, 36, and 40.

1. (currently amended) A method of [[to]] determining[[e]] 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 ~~thereof~~ for a patient in need of treatment for a nitrogen retention disorder selected from urea cycle disorder and hepatic 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~~ comprising (a) determining a target urinary phenylacetyl glutamine (PAGN) output based on a target nitrogen output and ~~determining from the~~ (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 to 75% ~~the effective dosage of the prodrug to produce a desired ammonia scavenging effect~~.

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 ~~the prodrug is HPN-100, and wherein~~ administration~~ering~~ of the effective initial dosage of PAA prodrug ~~HPN-100 to the patient~~ produces a normal plasma ammonia level in the patient.

5. (canceled)

6. (currently amended) A method of treating ~~to determine a dosage of a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof for~~ a patient having a nitrogen retention disorder selected from urea cycle disorder and hepatic encephalopathy~~, which~~ comprising[[es]] (a) determining a target ~~measuring~~ urinary ~~excretion~~

~~of~~ phenylacetyl glutamine (PAGN) output based on a target nitrogen output; (b) calculating an effective initial dosage of [[in]] a ~~patient to whom the~~ 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 ~~has been administered and calculating the dosage of the PAA prodrug based on a utilization efficiency for the~~ prodrug is calculated based on a mean conversion of PAA prodrug [[in]]to urinary PAGN of ~~about~~ 60% to ~~about~~ 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 nitrogen output takes into account ~~the dosage of the PAA prodrug is calculated from~~ the patient's dietary protein intake.

8. (currently amended) The method of claim 1 or 6 [[7]], wherein the target nitrogen output takes into account ~~dosage of the PAA prodrug is adjusted to account for~~ the patient's residual urea synthesis capacity.

9. (canceled)

10. (canceled)

11. (previously presented) The method of claim 1, wherein the PAA prodrug is HPN-100.

12-29. (canceled)

30. (currently amended) The method of claim 1, wherein the pharmaceutically acceptable salt of PBA ~~PAA prodrug~~ is sodium PBA ~~phenylbutyrate~~.

31. (previously presented) The method of claim 1, wherein the nitrogen retention disorder is urea cycle disorder.

32. (previously presented) The method of claim 1, wherein the nitrogen retention disorder is hepatic encephalopathy.

33. (previously presented) The method of claim 6, wherein the nitrogen retention disorder is urea cycle disorder.

34. (previously presented) The method of claim 6, wherein the nitrogen retention disorder is hepatic encephalopathy.

35. (previously presented) The method of claim 6, wherein the prodrug is HPN-100.

36. (canceled)

37. (currently amended) The method of claim 6, wherein the pharmaceutically acceptable salt of PBA ~~prodrug~~ is sodium PBA ~~phenylbutyrate~~.

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 ~~thereof~~ to a patient having a nitrogen retention disorder selected from urea cycle disorder and hepatic encephalopathy~~, the method~~ comprising (a) administering a first dosage of the PAA prodrug; (b) determining urinary phenylacetyl glutamine (PAGN) excretion ~~of the patient~~ following administration of the first dosage of the PAA prodrug[[,]]; (c) determining an effective dosage ~~dose~~ 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 ~~dose~~ to the patient.

39. (currently amended) The method of claim 38, wherein ~~the dosage of the PAA prodrug is based on a utilization efficiency for the PAA prodrug conversion into~~ urinary PAGN excretion is determined as a ratio of the concentration of urinary PAGN to urinary creatinine ~~of about 60% to about 75%.~~

(b) determining urinary phenylacetyl glutamine (PAGN) excretion

40. (canceled)

41. (currently amended) The method of claim 38, wherein the pharmaceutically acceptable salt of PBA is sodium PBA ~~phenylbutyrate is administered~~.

42. (currently amended) The method of claim 38, wherein the PAA prodrug is HPN-100 ~~is administered~~.

43. (previously presented) The method of claim 38, wherein the disorder is urea cycle disorder.

44. (previously presented) The method of claim 38, wherein the disorder is hepatic encephalopathy.

45. (currently amended) The method of claim 38 [[1]], wherein ~~the prodrug is sodium phenylbutyrate, and wherein~~ administration~~ering~~ of the effective dosage of PAA prodrug ~~the sodium phenylbutyrate to the patient~~ produces a normal plasma ammonia level in the patient.

Electronic Acknowledgement Receipt

EFS ID:	12127667
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-FEB-2012
Filing Date:	07-JAN-2009
Time Stamp:	22:31:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		OAResponse.pdf	81509 d401c4e30b5b58e81b2622a46a3b3ea39aa0a937	yes	16

	Multipart Description/PDF files in .zip description				
	Document Description	**Start**	**End**		
	Amendment After Final	1	1		
	Claims	2	5		
	Applicant Arguments/Remarks Made in an Amendment	6	16		
Warnings:					
Information:					
2	Rule 130, 131 or 132 Affidavits	Declaration.pdf	182035 872ee9f86301ea45605ee1318d38395b0ace025b	no	4
Warnings:					
Information:					
3	Non Patent Literature	Diaz2011.pdf	309128 cb344c07ae83a94d97619d2cd165cda5e0866180	no	1
Warnings:					
Information:					
4	Non Patent Literature	Lee2010.pdf	420728 ad8811066c7d3befc50a81761f6862275483f73d	no	9
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5	Non Patent Literature	Lichter2011.pdf	316417 6f554b82be07d240aea692fc1c28c69ee34436ca	no	7
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Information:					
6	Non Patent Literature	McGuire2010.pdf	526528 412460e2af908d0ed7661283389fc5bb97abb8e1	no	9
Warnings:					
Information:					
7	Non Patent Literature	1Ghabril2012.pdf	23156 9e157aeb3c756f343d60c4b0ab574b199bf06874	no	1
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		Total Files Size (in bytes):	1859501		

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New Applications Under 35 U.S.C. 111

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

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

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New International Application Filed with the USPTO as a Receiving Office

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Electronic Acknowledgement Receipt

EFS ID:	12137786
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:	22-FEB-2012
Filing Date:	07-JAN-2009
Time Stamp:	19:37:21
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	7917
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 [illegible] (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	IDs.pdf	615141 b164df4dbb35767b91da8d39194d47a8e60fecf0	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
2	Non Patent Literature	1Ghabril2012.pdf	23156 9e157aeb3c756f343d60c4b0ab574b199bf06874	no	1
Warnings:					
Information:					
3	Non Patent Literature	Diaz2011.pdf	309128 cb344c07ae83a94d97619d2cd165cda5e0866180	no	1
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Information:					
4	Non Patent Literature	Lee2010.pdf	420728 ad8811066c7d3befc50a81761f6862275483f73d	no	9
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Information:					
5	Non Patent Literature	Lichter2011.pdf	316417 6f554b82be07d240aea692fc1c28c69ee34436ca	no	7
Warnings:					
Information:					
6	Non Patent Literature	McGuire2010.pdf	526528 412460e2af908d0ed7661283389fc5bb97abb8e1	no	9
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Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	30579 da15d956538aa93621e439626da0714052356221	no	2
Warnings:					
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		Total Files Size (in bytes):	2241677		

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New International Application Filed with the USPTO as a Receiving Office

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