US009326966B2

(12) **United States Patent**
Scharschmidt et al.

(10) **Patent No.: US 9,326,966 B2**
(45) **Date of Patent: *May 3, 2016**

(54) **METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/958,259**

(22) Filed: **Dec. 3, 2015**

(65) **Prior Publication Data**

US 2016/0081969 A1 Mar. 24, 2016

Related U.S. Application Data

(63) Continuation of application No. 14/816,674, filed on Aug. 3, 2015, now Pat. No. 9,254,278, which is a continuation of application No. 13/775,000, filed on Feb. 22, 2013, now Pat. No. 9,095,559, which is a continuation of application No. 13/417,137, filed on Mar. 9, 2012, now Pat. No. 8,404,215.

(60) Provisional application No. 61/542,100, filed on Sep. 30, 2011, provisional application No. 61/564,668, filed on Nov. 29, 2011.

(51) **Int. Cl.**

A61K 49/00	(2006.01)
A61P 13/00	(2006.01)
A61K 31/235	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/235*** (2013.01); ***A61K 9/0053*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/216; G01N 31/221; Y10T 436/175383

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,284,647 A 8/1981 Brusilow et al.
4,457,942 A 7/1984 Brusilow

(Continued)

FOREIGN PATENT DOCUMENTS

WO WO94/22494 10/1994
WO WO2005/053607 6/2005

(Continued)

OTHER PUBLICATIONS

Ahrens, M. et al. (Jan. 2001). "Consensus Statement From a Conference for the Management of Patients With Urea Cycle Disorders." Supp. Journal of Pediatrics 138(1):S1-S5.

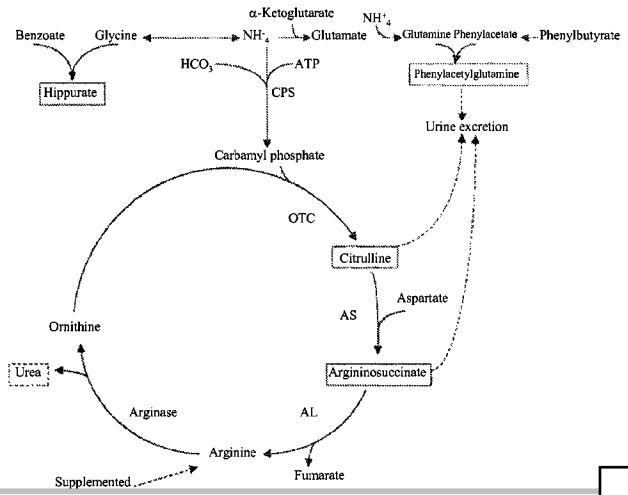
(Continued)

Primary Examiner — Savitha Rao

(57) **ABSTRACT**

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

15 Claims, 3 Drawing Sheets



(56) **References Cited**

U.S. PATENT DOCUMENTS

5,654,333	A	8/1997	Samid
5,968,979	A	10/1999	Brusilow
6,060,510	A	5/2000	Brusilow
6,083,984	A	7/2000	Brusilow
6,219,567	B1	4/2001	Eggers et al.
8,094,521	B2	1/2012	Levy
8,404,215	B1	3/2013	Scharschmidt et al.
8,642,012	B2	2/2014	Scharschmidt
9,078,865	B2	7/2015	Lee
2003/0195255	A1	10/2003	Summar
2004/0229948	A1	11/2004	Summar et al.
2005/0273359	A1	12/2005	Young
2006/0135612	A1	6/2006	Ferrante
2008/0119554	A1	5/2008	Jalan et al.
2010/0008859	A1	1/2010	Scharschmidt
2010/0016207	A1	1/2010	Wurtman et al.
2012/0022157	A1	1/2012	Scharschmidt
2012/0220661	A1	8/2012	Lee
2013/0210914	A1	8/2013	Scharschmidt et al.
2013/0281530	A1	10/2013	Scharschmidt et al.
2014/0142186	A1	5/2014	Scharschmidt et al.
2015/0094278	A1	4/2015	Scharschmidt et al.
2015/0105469	A1	4/2015	Scharschmidt et al.

FOREIGN PATENT DOCUMENTS

WO	WO2006/056794	6/2006
WO	WO2007/005633	1/2007
WO	WO2009/087474	7/2009
WO	WO2009/134460	11/2009
WO	WO2010/025303	3/2010
WO	WO2012/028620	3/2012
WO	WO2013/048558	4/2013
WO	WO2013/158145	10/2013

OTHER PUBLICATIONS

Ambrose, A.M. et al., "Further Studies on the Detoxification of Phenylacetic Acid", 101 J. Bio. Chem. 669 (1933).

Amodio, P., et al., "Detection of Minimal Hepatic Encephalopathy: Normalization and Optimization of the Psychometric Hepatic Encephalopathy Score. A Neuropsychological and Quantified EEG Study," J. Hepatol. 49:346-353 (2008).

Anda Notice Letter, Par Pharmaceutical, Inc. To Hyperion Therapeutics, inc.. Re: Glycerol Phenylbutyrate 1.1 gm/ml oral liquid; U.S. Pat. Nos. 8,404,215 and 8,642,012 Notice of Paragraph IV Certification Mar. 12, 2014.

Anda Notice Letter, Lupin Ltd. to Horizon Therapeutics, Inc.. Re: Notification of Invalidity, Unenforceability, and/or Noninfringement for U.S. Pat. Nos. 8,404,215 and 8,642,012 Pursuant to § 505(j)(2)(B)(ii) and (iv) of the Federal Food, Drug, and Cosmetic Act, Sep. 4, 2015.

Anda Notice Letter, Lupin Ltd. to Horizon Therapeutics, Inc.. Re: Notification of Invalidity, Unenforceability, and/or Noninfringement for U.S. Pat. No. 9,095,559 Pursuant to § 505(j)(2)(B)(ii) and (iv) of the Federal Food, Drug, and Cosmetic Act, Nov. 6, 2015.

Bajaj, J. S., et al., "Review Article: The Design of Clinical Trials in Hepatic Encephalopathy—An International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) Consensus Statement," Aliment Pharmacol Ther. 33 (7):739-747 (2011).

Barsotti, "Measurement of Ammonia in Blood", 138 J. Pediatrics, S11-S20 (2001).

Batshaw, M.L. et al., "Treatment of Inborn Errors of Urea Synthesis: Activation of Alternative Pathways of Waste Nitrogen Synthesis and Excretion", 306 N. Engl. J. Med. 1387 (1982).

Batshaw, M.L. et al., "New Approaches to the Diagnosis and Treatment of Inborn Errors of Urea Synthesis", 68 Pediatrics 290 (1981).

Batshaw, M.L. et al., "Treatment of Carbamyl Phosphate Synthetase Batshaw, M.L. et al., "Treatment of Hyperammonemic Coma Caused by Inborn Errors of Urea Synthesis", 97 J. Pediatrics 893 (1980).

Batshaw, M.L., "Hyperammonemia," Current Problems in Pediatrics, vol. 14, Issue 11, p. 6-69 (1984).

Batshaw, M. L. et. al., "Alternative Pathway Therapy for Urea Cycle Disorder: Twenty Years Later", 138 J. Pediatrics S46 (2001).

Berry, G. T. et al., "Long-Term Management of Patients with Urea Cycle Disorders", 138 J. Pediatrics S56 (2001).

Blau, Duran, Blaskovics, Gibson (editors), Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases, 261-276 (2d ed. 1996).

Blei, A. T., et al., "Hepatic Encephalopathy," Am. J. Gastroenterol. 96(7):1968-1976 (2001).

Brahe, C., et al., (2005) "Phenylbutyrate Increases SMN Gene Expression in Spinal Muscular Atrophy Patients," *Eur J Hum Genet* 13:256-259.

Brunetii-Pierri, N., et al., (2011) ""Phenylbutyrate Therapy for Maple Syrup Urine Disease"," Hum Mol Genet 20(4):631-640.

Brusilow, S.W. et al., "New Pathways of Nitrogen Excretion in Inborn Errors of Urea Synthesis", 2 Lancet 452 (1979).

Brusilow, S.W. et al., "Amino Acid Acylation: A Mechanism of Nitrogen Excretion in Inborn Errors of Urea Synthesis", 207 Science 659 (1980).

Brusilow, S.W., "Treatment of Episodic Hyperammonemia in Children With Inborn Errors of Urea Synthesis", 310 N. Engl. J. Med. 1630 (1984).

Brusilow, S.W. Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion, Pediatric Research, vol. 29, No. 2, 147-150 (1991).

Brusilow, S.W. et al, "Treatment of Urea Cycle Disorders", in Treatment of Genetic Diseases 79 (R.J. Desnik. et al., eds.1991).

Brusilow, S.W. et al., "Restoration of Nitrogen Homeostasis in a Man with Ornithine Transcarbamylase Deficiency", 42 J. Metabolism 1336 (1993).

Brusilow, S.W., "Protocols for Management of Intercurrent Hyperammonemia in Patients with Urea Cycle Disorders", FDA Application to Market a New Drug for Human Use or an Antibiotic Drug for Human Use, Fourteen pages (Amendment Dated Jul. 25, 1994).

Brusilow, S.W. et al., "Urea Cycle Disorders: Clinical Paradigm of Hyperammonemic Encephalopathy", 12 Progress in Liver Diseases 293 (1995).

Brusilow, S.W. et al., "Urea Cycle Enzymes", in the Metabolic and Molecular Bases of Inherited Diseases 1187 (C.R. Scriver et al. eds. 1995).

Brusilow, S.W. et al., "Urea Cycle Disorders: Diagnosis, Pathophysiology, and Therapy", 43 Adv. Pediatr. 127 (1996).

Burlina, A.B. et al., "Long-Term Treatment with Sodium Phenylbutyrate in Ornithine Transcarbamylase-Deficient Patients", 72 Molecular Genetics and Metabolism 351-355 (2001).

Calloway, D.H. et al., "Sweat and Miscellaneous Nitrogen Losses in Human Balance Studies", 101 J. Nutrition 775 (1971).

Calloway, D.H. et al., "Variation in Endogenous Nitrogen Excretion and Dietary Nitrogen Utilization as Determinants of Human Protein Requirements", 101 J. Nutrition 205 (1971).

Camacho, L.H. et al., "Phase I Dose Escalation Clinical Trial of Phenylbutyrate Sodium Administered Twice Daily to Patients With Advanced Solid Tumors", 25 Invest. New Drugs 131 (2007, e-pub. Oct. 20, 2006).

Carducci, M., "Phenylbutyrate Induces Apoptosis in Human Prostate Cancer and is More Potent Than Phenylacetate", 2 Clinical Cancer Research 379 (1996).

Carducci, M.A. et al., "A Phase I Clinical and Pharmacological Evaluation of Sodium Phenylbutyrate on an 120-h Infusion Schedule", 7 Clin. Cancer Res. 3047 (2001).

Center for Drug Evaluation and Research, Clinical Pharmacology and Biopharmaceutics Review for New Drug Application No. 20-645 (Ammonul®) (2005).

Center for Drug Evaluation and Research, Labeling for New Drug Application No. 20-645 (Ammonul®) (2005).

Center for Drug Evaluation and Research, Medical Review for New Drug Application No. 20-645 (Ammonul®) (2005).

(56) **References Cited**

OTHER PUBLICATIONS

Chen, Z. et al., "Tributyrin: A Prodrug of Butyric Acid for Potential Clinical Application in Differentiation Therapy", 54 Cancer Research 3494 (1994).
Chung, Y.L., et al., (2000) "A Novel Approach for Nasopharyngeal Carcinoma Treatment Uese Phenylbutyrate as a Protein Kinase C Modulator: Implications for Radiosensitization and EBV-Targeted Therapy," Clin Cancer Res 6:1452-1458.
Clay, A. et. al, "Hyperammonemia in the ICU", 132 Chest 1368 (2007).
ClinicalTrials.Gov/Archive View of NCT00551200 on Dec. 11, 2007, Dose-Escalation Safety Study of Glyceryl Tri (4-Phenylbutyrate)(GT4P) to Treat Urea Cycle Disorders, [accessed Oct. 5, 2009], 4 pages.
Collins, A.F. et al., "Oral Sodium Phenylbutyrate Therapy in Homozygous Beta Thalassemia: A Clinical Trial", 85 Blood 43 (1995).
Combined Search and Examination Report mailed on Oct. 9, 2009, for Great Britain Patent Application No. GB0915545.8, filed on Aug. 27, 2009, eight pages.
Combined Search and Examination Report mailed on Sep. 9, 2010, for Great Britain Patent Application No. 1013468.2, filed on Aug. 27, 2009, six pages.
'Complaint for Patent Infringement', *Hyperion Therapeutics, Inc.* v. *Par Pharmaceuticals, Inc.* Filed in U.S. District Court for the Eastern District of Texas, Apr. 23, 2014.
'Complaint for Patent Infringement', *Horizon Therapeutics, Inc.* v. *Lupin Ltd. and Lupin Pharmaceuticals Inc.* Filed in U.S. District Court for the District of New Jersey, Oct. 19, 2015.
Comte, B., et al., "Identification of Phenylbutyrylglutamine, A New Metabolite of Phenylbutyrate Metabolism in Humans", 37 J. Mass Spectrometry 581 (2002).
Conn, H. O., et al., "Liver Physiology and Disease: Comparison of Lactulose and Neomycin in the Treatment of Chronic Portal-Systemic Encephalopathy. A Double Blind Controlled Trial," Gastroenterology 72(4):573-583 (1977).
Cordoba, J., "New Assessment of Hepatic Encephalopathy," Journal of Hepatology 54: 1030-1040 (2011).
Cudrowicz (2009) "Phase 2 Study of Sodium Phenylbutyrate in ALS," Amyotrophic Lateral Sclerosis 10:99-106.
Darmaun, D. et al., "Phenylbutyrate-Induced Glutamine Depletion in Humans: Effect on Leucine Metabolism", 5 Am. J. of Physiology: Endocrinology and Metabolism E801 (1998).
Darzens, G. et al.: "Preparation de quelques glycerides phenylaliphatiques et leur reduction en alcools . . . ", Comptes Rendus Hebdomadaires Des Seances De L'Academie Des Sciences., vol. 205, Oct. 18, 1937, pp. 682-684.
Deferrari, G. et al., "Brain Metabolism of Amino Acids and Ammonia in Patients with Chronic Renal Insufficiency", 20 Kidney International 505 (1981).
Diaz, G.A. et al., "Phase 3 Blinded, Randomized, Crossover Comparison of Sodium Phenylbutyrate (NaPBA) and Glycerol Phenylbutyrate (GPB): Ammonia (NH3) Control in Adults with Urea Cycle Disorders (UCDs)", 102 Mol. Genet. Metab. 276 (1981), Society of Inherited Metabolic Disease (SMID) Abstract, (2011).
Diaz G.A.et al, "Ammonia (NH3) control and improved neurocognitive outcome among urea cycle disorder (UCD) patients treated with glycerol phenylbutyrate (GPB)." Mol. Genet. Metab. 2012, 105, 311, SIMD Abstract 24.
Diaz, G. A., et al., "Ammonia Control and Neurocognitive Outcome Among Urea Cycle Disorder Patients Treated with Glycerol Phenylbutyrate," Hepatology 57(6):2171-2179 (2013).
Dixon, M. A. and Leonard, J.V., "Intercurrent Illness in Inborn Errors of Intermediary Metabolism, 67 Archives of Disease in Childhood", 1387 (1992).
Dover, G. et al, "Induction of Fetal Hemoglobin Production in Sub-
Endo, F. et al., "Clinical Manifestations of Inborn Errors of the Urea Cycle and Related Metabolic Disorders During Childhood", 134 J. Nutrition 1605S (2004).
Enns, G. M., et al., "Survival After Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders", 356 N. Eng. J. Med. 2282 (2007).
European Medicines Agency, Annex I: Summary of Product Characteristics for Ammonaps.
European Medicines Agency, European Public Assessment Report: Summary for the Public for Ammonaps (2009).
European Medicines Agency, Scientific Discussion for Ammonaps (2005).
European Medicines Agency, Scientific Discussion for Carbaglu (2004).
European Patent Office, Extended European Search Report for EP09739263 completed Nov. 2, 2011.
European Patent Office, International Search Report and Written Opinion for PCT/US2009/055256 completed Dec. 18, 2009 and mailed Dec. 30, 2009.
Examination Report mailed Feb. 5, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on Aug. 27, 2009, two pages.
Examination Report mailed May 11, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on Aug. 27, 2009, one page.
Examination Report mailed on Oct. 27, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on Aug. 27, 2009, two pages.
Examination Report for British Patent Application No. GB1013468.2 dated Oct. 28, 2011.
FDA Label for Ammonul®, sixteen pages (Feb. 2005).
FDA Label for Buphenyl, six pages.
FDA Buphenyl® (Sodium Phenylbutyrate) Label, nine pages. (Aug. 2003).
FDA Label for Carbaglu, seven pages. (Mar. 2010).
Feillet, F. and Leonard, J.V., "Alternative Pathway Therapy for Urea Cycle Disorders", 21 J. Inher. Metab. Dis. 101-111 (1998).
Feoli-Fonseca, M. L., "Sodium Benzoate Therapy in Children with Inborn Errors of Urea Synthesis: Effect on Carnitine Metabolism and Ammonia Nitrogen Removal", 57 Biochemical and Molecular Medicine 31 (1996).
Ferenci, P., et al., "Hepatic Encephalopathy-Definition, Nomenclature, Diagnosis, and Quantification: Final Report of the Working Party at the 11th World Congresses of Gastroenterology, Vienna, 1998," Hepatology 35:716-721 (2002).
Fernandes, Saudubray, Berghe (editors), "Inborn Metabolic Diseases Diagnosis and Treatment", 219-222 (3d ed. 2000).
Gargosky, S. "Improved Survival of Neonates Following Administration of Ammonul® (Sodium Phenyl acetate & Sodium Benzoate) 10% 110% Injection", SSIEM Poster, six pages (Aug. 2, 2005).
Gargosky, S. et al., "Results of a Twenty-two Year Clinical Trial: Acute, Adjunctive Pharmacological Treatment of Hyperammonemic Episodes in Patients with Deficiencies in Enzymes of the Urea Cycle", poster, Ucyclyd Pharma, Inc., one page (Oct. 14, 2005).
Gargosky, S., "High Ammonia Levels are Associated With Increased Mortality and Coma", Ucyclyd Pharma, Inc., one page (2006).
Geraghty, M.T. and Brusilow, S.W., Disorders of the Urea Cycle, in Liver Disease in Children 827 (F.J. Suchy et al., eds. 2001).
Ghabril, M. et al., Glycerol Phenylbutyrate (GPB) Administration in Patients with Cirrhosis and Episodic Hepatic Encephalopathy (HE), accepted for presentation at Digestive Disease Week (2012).
Ghabril, M. et al., "Glycerol Phenylbutyrate in Patients with Cirrhosis and Episodic Hepatic Encephalopathy: A Pilot Study of Safety and Effect on Venous Ammonia Concentration," Clinical Pharmacology in Drug Development 2(3): 278-284 (2013).
Gilbert, J. et al., "A Phase I Dose Escalation and Bioavailability Study of Oral Sodium Phenylbutyrate in Patients with Refractory Solid Tumor Malignancies", 7 Clin. Cancer Research 2292-2300 (2001).
Gore, S. et al., "Impact of the Putative Differentiating Agent Sodium Phenylbutyrate on Myelodysplastic Syndromes and Acute Myeloid Leukemia", 7 Clin. Cancer Res. 2330 (2001).

(56) **References Cited**

OTHER PUBLICATIONS

Gropman, A. L. et al., 1H MRS Allows Brain Phenotype Differentiation in Sisters with Late Onset Ornithine Transcarbamylase Deficiency (OTCD) and Discordant Clinical Presentations, 94 Mol. Genet. Metab. 52 (2008).
Gropman, A.L. et al., 1H MRS Identifies Symptomatic and Asymptomatic Subjects With Partial Ornithine Transcarbamylase Deficiency, 95 Mol. Genet. Metab. 21 (Sep.-Oct. 2008, e-pub. Jul. 26, 2008).
Gropman, A. (2010) "Brain Imaging in Urea Cycle Disorders," Mol Genet Metab 100:S20-S30.
Hassanein, T. I., et al., "Randomized Controlled Study of Extracorporeal Albumin Dialysis for Hepatic Encephalopathy in Advanced Cirrhosis," Hepatology 46:1853-1862 (2007).
Hassanein, T. I., et al., "Introduction to the Hepatic Encephalopathy Scoring Algorithm (HESA)," Dig. Dis. Sci. 53:529-538 (2008).
Hassanein, T., et al., "Performance of the Hepatic Encephalopathy Scoring Algorithm in a Clinical Trial of Patients With Cirrhosis and Severe Hepatic Encephalopathy," Am. J. Gastroenterol. 104:1392-1400 (2009).
Hines, P., et al., (2008) "Pulsed-Dosing with Oral Sodium Phenylbutyrate Increases Hemoglobin F in a Patient with Sickle Cell Anemia," Pediatr Blood Cancer 50:357-359.
Hogarth, P., et al., (2007) "Sodium Phenylbutyrate in Huntington's Disease: A Dose-Finding Study," Mov Disord 22(13):1962-1964.
Honda, S. et al., "Successful Treatment of Severe Hyperammonemia Using Sodium Phenylacetate Power Prepared in Hospital Pharmacy", 25 Biol. Pharm. Bull. 1244 (2002).
Huang, H.H., et al., (2012) "Cannabinoid Receptor 2 Agonist Ameliorates Mesenteric Angiogenesis and Portosystemic Collaterals in Cirrhotic Rats," Hepatology 56:248-258.
Hyperion Therapeutics. "Hyperion Therapeutics Announces Enrollment of First Patient in Phase 1/2 Clinical Trial of GT4P in Patients with Urea Cycle Disorders" Announcement, 1 page (Oct. 23, 2007).
Hyperion Therapeutics. (Jun. 2, 2009.) Hyperion Therapeutics Announces Results of Phase I Study in Patients with Liver Cirrhosis, located at <http://www.hyperiontx.com/press/release/pr-1243891161>, last visited on Apr. 27, 2011, three pages.
Hyperion Therapeutics. (Mar. 30, 2009).,Hyperion Therapeutics Announces Results for Phase II Study in Urea Cycle Disorders, located at <http://www.hyperiontx.com/press/release/pr1238518388,> last visited on Apr. 27, 2011, three pages.
International Preliminary Report on Patentability mailed on Mar. 1, 2011, for PCT Application No. PCT/US2009/030362, filed on Jan. 7, 2009, seven pages.
International Preliminary Report on Patentability mailed on Mar. 1, 2011, for PCT Application No. PCT/US2009/055256, filed on Aug. 27, 2009, six pages.
International Search Report and Written Opinion for PCT/US09/30362, mailed Mar. 2, 2009, 8 pages.
International Search Report and Written Opinion for PCT/US2009/055256, mailed Dec. 30, 2009, 13 pages.
International Preliminary Report on Patentability (Ch I) for PCT/US2012/028620 completed Jun. 4, 2012 and mailed on Apr. 10, 2014.
International Preliminary Report on Patentability (Ch II) for PCT/US2012/028620, completed Aug. 22, 2013 and mailed Sep. 4, 2013.
Inter Partes Review of U.S. Pat. No. 8,404,215.
Inter Partes Review of U.S. Pat. No. 8,642,012.
James, M.O. et al., "The Conjugation of Phenylacetic Acid in Man, Sub-Human Primates and Some Other Non-Primates Species", 182 Proc. R. Soc. London 25 (1972).
John, B.A. et al., "The Disposition of HPN-100, A Novel Pharmaceutical Under Development for Potential Treatment of Hyperammonemia, in Cynomolgus Monkeys", ACMG 2009 ADME, poster, two pages (Mar. 2009).
John, BA et al. (Mar. 2009). "The Disposition of HPN-100, A Novel Pharmaceutical Under Development for Potential Treatment of
Kasumov T., et al., "New Secondary Metabolites of Phenylbutyrate in Humans and Rats", 32 Drug Metabolism and Disposition 10 (2004).
Kleppe, S. et al., "Urea Cycle Disorders", 5 Current Treatment Options in Neurology 309-319 (2003).
Kubota, K. and Ishizaki, T., Dose-Dependent Pharmacokinetics of Benzoic Acid Following Oral Administration of Sodium Benzoate to Humans, 41 Eur. J. Clin. Pharmacol. 363 (1991).
Lea et al., "Butyramide and Monobutyrin: Growth Inhibitory and Differentiating Agents", Anticancer Res., 13: 145-150 (1993).
Lee, B. and Goss, J., "Long-Term Correction of Urea Cycle Disorders", 138 J. Pediatrics S62 (2001).
Lee, B. et al., "Considerations in the Difficult-to-Manage Urea Cycle Disorder Patient", 21 Crit. Care Clin. S19 (2005).
Lee, B. et al. (Aug. 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.
Lee, B. et al., "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)", presented at ICIEM 2009, San Diego, CA, poster, one page. (Aug. 2009).
Lee, B. et al., "Phase 2 Study of a Novel Ammonia Scavenging Agent in Adults With Urea Cycle Disorders (UCDs)", abstract presented at ACMG 2009, one page. (Mar. 2009).
Lee, B. et al., "Phase 2 Study of a Novel Ammonia Scavenging Agent in Adults with Urea Cycle Disorders (UCDs)", presented at ACMG 2009, seventeen pages (Mar. 2009).
Lee B. et al., "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. (Aug. 2008).
Lee, B. et al., "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 (Sep. 2008).
Lee, B., et al., "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])", 31 J. Inherit. Metab. Dis. 91 (2008).
Lee, B., et al., Phase 2 Comparison of a Novel Ammonia Scavenging Agent with Sodium Phenylbutyrate in Patients with Urea Cycle Disorders: Safety, Pharmacokinetics and Ammonia Control, 100 Mol. Genet. Metab. 221 (2010).
Lee, B., et al., "Optimizing Ammonia (NH3) Control in Urea Cycle Disorder (UCD) Patients: A Predictive Model," Oral Abstract Platform Presentations, Biochemical Genetics, Phoenix, AZ, Mar. 22, 2013.
Leonard, J.V., "Urea Cycle Disorders", 7 Semin. Nenatol. 27 (2002).
Levin, B. et al. "Hyperammonaemia: A Variant Type of Deficiency of Ornithinine Transcarbamylase." Arch. Dis. Childhd. 1969, 44, 162-169.
Lewis, H.B., "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", 18 J. Biol. Chem. 225 (1914).
Liang, K.Y., et al., "Longitudinal Data Analysis Using Generalized Linear Models", 73 Biometrika 13 (1986).
Lichter-Konecki, U., et al., "Ammonia Control in Children with Urea Cycle Disorders (UCDs); Phase 2 Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate", 103 Mol. Genet. Metab. 323 (2011).

(56) **References Cited**

OTHER PUBLICATIONS

Macarthur, H B., et al., "Pharmacokinetics of Sodium Phenylacetate and Sodium Benzoate Following Intravenous Administration as Both a Bolus and Continuous Infusion to Healthy Adult Volunteers", 81 Mol. Genet. Metab. S67 (2004).
Maestri, N.E., et al., "Prospective treatment of urea cycle disorders", J Paediatr 1991;119:923-928.
Maestri, N.E. et al., "Plasma Glutamine Concentration: A Guide in the Management of Urea Cycle Disorders", 121 J. Pediatrics 259 (1992).
Maestri, N.E., et al., "Long-Term Survival of Patients with Argininosuccinate Synthetase Deficiency", 127 J. Pediatrics 929 (1993).
Maestri, N.E., "Long-Term Treatment of Girls with Ornithine Transcarbamylase Deficiency", 355 N. Engl. J. Med. 855 (1996).
Majeed, K., "Hyperammonemia", eMedicine.com (Dec. 2001).
Mansour, A. et al., "Abdominal Operations in Patients with Cirrhosis: Still a Major Surgical Challenge", 122 Surgery 730 (1997) (Abstract Only).
Marini, J.C. et al., "Phenylbutyrate Improves Nitrogen Disposal via an Alternative Pathway without Eliciting an Increase in Protein Breakdown and Catabolism in Control and Ornithine Transcarbamylase-Deficient Patients", 93 Am. J. Clin. Nutr. 1248 (2011).
Matsuda, I., "Hyperammonemia in Pediatric Clinics: A Review of Ornithine Transcarbamylase Deficiency (OTCD) Based on our Case Studies", 47 JMAJ 160 (2004).
McGuire, B. et al., "Pharmacokinetic (PK) Safety Study of Sodium Phenylacetate and Sodium Benzoate Administered to Subjects with Hepatic Impairment", abstract of the 13th International Symposium, Abano (Padova), Italy, Apr. 28-May 1, 2008, two pages (Apr. 2008).
McGuire, B. et al., "Pharmacokinetic Safety Study of Sodium Phenylacetate and Sodium Benzoate Administered to Subjects With Hepatic Impairments", 28 Liver International 743 (2008) (Abstract Only).
McGuire, B.M. et al., "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 (May 2009).
McGuire, B.M. et al., "Pharmacokinetic (PK) and Safety Analyses of a Novel Ammonia-Reducing Agent in Healthy Adults and Patients with Cirrhosis", Hyperion Therapeutics, poster, one page (2009).
McGuire, B. M., et al., "Pharmacology and Safety of Glycerol Phenylbutyrate in Healthy Adults and Adults with Cirrhosis", 51 Hepatol. 2077 (2010).
McQuade, P.S., "Analysis and the Effects of Some Drugs on the Metabolism of Phenylethylamine and Phenylacetic Acid", 8 Neuropsychopharmacol. Bio. Psychiat.607 (1984).
Mercuri, E., et al., (2004) "Pilot Trial of Phenylbutyrate in Spinal Muscular Atrophy," Neuromuscul Disord 14:130-135.
Mizutani, N. et al., "Hyperargininemia: Clinical Course and Treatment with Sodium Benzoate and Phenylacetic Acid", 5 Brain and Development 555 (1983).
Mokhtarani, M., et al., (2012) "Elevated Phenylacetic Acid (PAA) Levels Appear Linked to Neurological Adverse Events in Healthy Adults But Not in Urea Cycle Disorder (UCD) Patients," Mol Genet Metab 105:342.
Mokhtarani, M., et al., (2013) "Elevated Phenylacetic Acid Levels Do Not Correlate with Adverse Events in Patients with Urea Cycle Disorders o rHepatic Encephalopathy and Can Be Predicted Based on the Plasma PAA to PAGN Ratio," Mol Genet Metab 110(4):446-453.
Mokhtarani et al., (2012) "Urinary phenylacetylglutamine appears to be a more useful marker than metabolite blood levels for therapeutic monitoring of phenylacetic acid (PAA) prodrugs." Mol Genet Metab 105, 312, SIMD Abstract 78.
Mokhtarani, M., et al., (2012) "Urinary Phenylacetylglutamine as Dosing Biomarker for Patients with Urea Cycle Disorders," Mol Genet Metab 107(3):308-314.
Monteleone, JPR, et al., (2012) "Population pk Analysis of Glycerol Phenylbutyrate (GPB) and Sodium Phenylbutyrate(NAPBA) in Adult and Pediatric Patients with Urea Cycle Discarders," Mol Genet Metab 105:343.
Monteleone, JPR, et al., (2013) "Population Pharmacokinetic Modeling and Dosing Simulations of Nitrogen-Scavenging Compounds: Disposition of Glycerol Phenylbutyrate and Sodium Phenylbutyrate in Adult and Pediatric Patients with Urea Cycle Disorders," J. Clin. Pharmacol. 53(7): 699-710.
Munoz, S. J., "Hepatic Encephalopathy," Med, Clin. N. Am. 92:795-812 (2008).
Nassogne, M.C., "Urea Cycle Defects: Management and Outcome", 28 J. Inherit. Metab. Dis. 407 (2005).
New England Consortium of Metabolic Programs, Acute Illness Protocol: Urea Cycle Disorders: The Infant/Child with Argininosuccinate Lyase Deficiency, adapted from Summar, M and Tuchman, M, Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders, 138 J. Peds. Suppl. S6 (2001).
New England Consortium of Metabolic Programs, Acute Illness Protocol: Urea Cycle Disorders: The Infant/Child with Citrullinemia, adapted from Summar, M and Tuchman, M, Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders, 138 J. Peds. Suppl. S6 (2001).
Newmark, H. L. and Young, W. C., "Butyrate and Phenylacetate as Differentiating Agents: Practical Problems and Opportunities", 22 J. Cellular Biochemistry 247 (1995).
Ong, J. P., et al., (2003) "Correlation Between Ammonia Levels and the Severity of Hepatic Encephalopathy," Am. J. Med. 114:188-193.
Ortiz, M., et al., "Development of a Clinical Hepatic Encephalopathy Staging Scale," Aliment Pharmacol Ther 26:859-867 (2007).
PAR Pharmaceutical, Inc.'S Initial Invalidity Contentions and Non-Infringement Contentions for U.S. Pat. Nos. 8,404,215 and 8,642,012.
Parsons-Smith, B. G., et al., "The Electroencephalograph in Liver Disease," Lancet 273:867-871 (1957).
Perrine, S. P., (2008) "Fetal Globin Stimulant Therapies in the Beta-Hemoglobinopathies: Principles and Current Potential," Pediatr Ann 37(5):339-346.
Phuphanich, S. et al., "Oral Sodium Phenylbutyrate in Patients with Recurrent Malignant Gliomas: A Dose Escalation and Pharmacologic Study", Neuro-Oncology 177 (2005).
Piscitelli, S.C. et al., "Disposition of Phenylbutyrate and its Metabolites, Phenylacetate and Phenylacetylglutamine", 35 J. Clin. Pharmacology 368 (1995).
Praphanproj, V. et al., "Three Cases of Intravenous Sodium Benzoate and Sodium Phenylacetate Toxicity Occurring in the Treatment of Acute Hyperammonemia," 23 J. Inherited Metabolic Disease 129 (2000).
Propst, A. et al., "Prognosis and Life Expectancy in Chronic Liver Disease", 40 Dig Dis Sci 1805 (1995) (Abstract Only).
Riley, T.R. et al., "Preventive Strategies in Chronic Liver Disease: Part II", Cirrhosis, 64 Am. Earn. Physician 1735 (2001). (Abstract Only).
Rockey, D. C., et al., "Randomized, Controlled, Double Blind Study of Glycerol Phenylbutyrate in Patients with Cirrhosis and Episodic Hepatic Encephalopathy," Hepatology 56:248(A) (2012).
Rudman, D., et al., "Maximal Rates of Excretion and Synthesis of Urea in Normal and Cirrhotic Subjects", 52 J. Clin. Invest. 2241 (1973).
Ryu, H., et al., (2005) "Sodium Phenylbutyrate Prolongs Survival and Regulates Expression of Anti-Apoptotic Genes in Transgenic Amyotrophic Lateral Sclerosis Mice," J Neurochem 93:1087-1098.
Salam, M., et al., "Modified-Orientation Log to Assess Hepatic Encephalopathy," Aliment Pharmacol Ther. 35(8):913-920 (2012).
Scientific Discussion for Ammonaps, EMEA 2005, available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000219/WC500024748.pdf.

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