US009561197B2

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

(10) **Patent No.: US 9,561,197 B2**
(45) **Date of Patent: *Feb. 7, 2017**

(54) **METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS**

(75) Inventors: **Bruce Scharschmidt**, San Francisco, CA (US); **Masoud Mokhtarani**, Walnut Creek, CA (US)

(73) Assignee: **Horizon Therapeutics, LLC**, Lake Forest, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 649 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/610,580**

(22) Filed: **Sep. 11, 2012**

(65) **Prior Publication Data**

US 2013/0281530 A1 Oct. 24, 2013

Related U.S. Application Data

(60) Provisional application No. 61/636,256, filed on Apr. 20, 2012.

(51) **Int. Cl.**

A61K 31/192	(2006.01)
A61K 31/216	(2006.01)
A61K 31/225	(2006.01)
G01N 33/68	(2006.01)

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

CPC ***A61K 31/192*** (2013.01); ***A61K 31/216*** (2013.01); ***G01N 33/6812*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/192; A61K 31/216

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,284,647	A	8/1981	Brusilow
4,457,942	A	7/1984	Brusilow
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
8,094,521	B2	1/2012	Levy
8,404,215	B1	3/2013	Scharschmidt et al.
8,642,012	B2	2/2014	Scharschmidt
2003/0195255	A1	10/2003	Summar
2004/0229948	A1	11/2004	Summar
2005/0273359	A1	12/2005	Young
2006/0135612	A1	6/2006	Ferrante
2008/0119554	A1	5/2008	Jalan
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
2014/0142186	A1	5/2014	Scharschmidt et al.

FOREIGN PATENT DOCUMENTS

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

OTHER PUBLICATIONS

Ambrose, A.M., (1933) "Further Studies on the Detoxification of Phyenylacetic Acid." *J Biol Chem* 101:669-675.

Batshaw M.L. et al. (Dec. 1980) "Treatment of Hyperammonemic Coma Caused by Inborn Errors of Urea Synthesis," *J Pediatr* 97(6):893-900.

Batshaw M.L. et al. (Jun. 10, 1982) "Treatment of Inborn Errors of Urea Synthesis: Activation of Alternative Pathways of Waste Nitrogen Synthesis and Excretion," *N. Engl J Med* 306(23):1387-1392.

Batshaw, M.L. (1984) "Hyperammonemia," in Current Problems in Pediatrics, Lockhart, J.D. ed.: Year Book Medical Publishers, pp. 2-69.

Batshaw, M.L. et al. (Aug. 1981) "New Approaches to the Diagnosis and Treatment of Inborn Errors of Urea Synthesis," *Pediatrics* 68(2):290-297.

Berry, G.T. et al., (2001) "Long-term Management of Patients with Urea Cycle Disorders." *J Pediatrics* 138:S56-S61.

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

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

Brusilow, S.W., et al. (Sep. 1, 1979) "New Pathways of Nitrogen Excretion in Inborn Errors of Urea Synthesis," *Lancet* 2(8140):452-454.

Brusilow, S.W., et al. (Feb. 8, 1980) "Amino Acid Acylation: A Mechanism of Nitrogen Excretion in Inborn Errors of Urea Synthesis," *Science* 207:659-661.

Brusilow, S.W., et al. (Jun. 21, 1984) "Treatment of Episodic Hyperammonemia in Children With Inborn Errors of Urea Synthesis," *N. Engl J Med* 310(25):1630-1634.

Brusilow, S.W., et al. (1991) Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion. *Pediatric Res* 29(2):147-150.

Brusilow, S.W., et al. (1991) "Treatment of Urea Cycle Disorders," Chapter 5 in Treatment of Genetic Diseases, Desnik, R.J. et al. eds, Churchill Livingstone, New York, New York, pp. 79-94.

Brusilow, S.W., et al. (1993) "Restoration of Nitrogen Homeostasis in a Man with Ornithine Transcarbamylase Deficiency." *J Metabolism* 42:1336-1339.

Brusilow, S.W., et al. (Jul. 25, 1994—Amendment Dated) "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, 14 pages.

Brusilow, S.W., et al. (1995) "Urea Cycle Disorders: Clinical Paradigm of Hyperammonemic Encephalopathy." *Prog Liver Diseases* 12:293-309.

Brusilow, S.W., et al. (1995) "Urea Cycle Enzymes," Chapter 32 in The Metabolic and Molecular bases of Inherited Diseases, Scriver, C.R. et al. eds., McGraw-Hill, Inc. New York, New York, pp. 1187-1232.

(Continued)

Primary Examiner — Jeffrey S Lundgren
Assistant Examiner — Sara E Townsley

(57) **ABSTRACT**

The present disclosure provides methods for adjusting the dosage of PAA prodrugs (e.g., HPN-100, PBA) based on measurement of PAA and PAGN in plasma and calculating the PAA:PAGN ratio so as to determine whether PAA to PAGN conversion is saturated

(56) **References Cited**

OTHER PUBLICATIONS

Brusilow, S.W., et al. (1996) "Urea Cycle Disorders: Diagnosis, Pathophysiology, and Therapy," *Adv Pediatr* 43:127-170.
Calloway, D.H. et al. (1971) "Sweat and Miscellaneous Nitrogen Losses in Human Balance Studies," *J Nutrition* 101:775-786.
Calloway, D.H. et al. (1971) "Variation in Endogenous Nitrogen Excretion and Dietary Nitrogen Utilization as Determinants of Human Protein Requirements," *J Nutrition* 101:205-216.
Camacho, L.H. et al. "Phase I Dose Escalation Clinical Trial of Phenyl butyrate Sodium Administered Twice Daily to Patients With Advanced Solid Tumors," *Invest. New Drugs* 25:131-138 (2007, e-pub. Oct. 20, 2006).
Chang, J. et al., (2001) "Treatment of Spinal Muscular Atrophy by Sodium Butyrate," *PNAS* 98(17):9808-9813.
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.
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.
Comte, B. et al., (2002) "Identification of Phenylbutyrylglutamine, a new Metabolite of Phenylbutyrate Metabolism in Humans," *J Mass Spectrometry*, 37(6):581-590.
Cudkowicz, ALS (2009) "Phase 2 Study of Sodium Phenylbutyrate in ALS," *Amyotrophic Lateral Sclerosis* 10:99-106.
Deferrari, G. et al. (1981) "Brain Metabolism of Amino Acids and Ammonia in Patients with Chronic Renal Insufficiency," *Kidney International* 20:505-510.
Diaz, G.A., et al., (2011) "Phase 3 Blinded, Randomized, Crossover Comparison of Sodium Phenylbutyrate (NaPBA) and Glycerol Phenylbutyrate (GPB): Ammonia (NH3) Control in Adults with Urea Cycle Disorders (UCDs)," *Mol. Genet. Metab*. 102:276.
Diaz, G.A.. et al.. "Phase 3 Blinded. Randomized, Crossover Comparison of Sodium Phenylbutyrate (NaPBA) and Glycerol Phenylbutyrate (GPB): Ammonia (NH3) Control in Adults with Urea Cycle Disorders (UCDs)," *Mol. Genet. Metab*. 102:276, *Society of Inherited Metabolic Disease* (SMID) Abstract.
Enns, G.M., et al., (2007) "Survival After Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders," *N. Eng J Med* 356:2282-2292.
FDA Label for Buphenyl, 6 pages.
FDA. "Buphenyl® (Sodium Phenylbutyrate) Label" nine pages (Aug. 2003).
Gargosky, S. (Aug. 2, 2005) "Improved Survival of Neonates Following Administration of Ammonul® (Sodium Phenyl acetate & Sodium Benzoate) 10% I 10% Injection," SSIEM Poster, six pages.
Gargosky, S. et al. (Oct. 14, 2005) "Results of a Twenty-two Year Clinical Trial: Actue, Adjunctive Pharmacological Treatment of Hyperammonemic Episodes in Patients with Deficiencies in Enzymes of the Urea Cycle," poster, Ucyclyd Pharma, Inc., one page.
Gargosky, S. (2006) "High Ammonia Levels Are Associated With Increased Mortality and Coma," Ucyclyd Pharma, Inc., one page.
Ghabril, M., et al., (2012) "Glycerol Phenylbutyrate (GPB) Administration in Patients with Cirrhosis and Episodic Hepatic Encephalopathy (HE)," accepted for presentation at Digestive Disease Week.
Gropman, A.L., et al., (2008) "1H MRS Allows Brain Phenotype Differentiation in Sisters with Late Onset Ornithine Transcarbamylase Deficiency (OTCD) and Discordant Clinical Presentations," *Mol Genet Metab* 94(1):52-60.
Gropman, A.L. et al. (2008) "1H MRS Identifies Symptomatic and Asymptomatic Subjects With Partial Ornithine Transcarbamylase Deficiency," *Mol Genet Metab* 95(1-2):21-30 (Sep.-Oct. 2008, e-pub. Jul. 26, 2008).
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.
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 (Oct. 23, 2007) "Hyperion Therapeutics Announces Enrollment of First Patient in Phase 1/2 Clinical Trial of GT4P in Patients with Urea Cycle Disorders" Announcement, 1 page.
Hyperion Therapeutics. "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 (Mar. 30, 2009).
Hyperion Therapeutics. "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 (Jun. 2, 2009).
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.
John, B.A. et al. (Mar. 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.
John, B.A. et al. (Mar. 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.
Kasumov, T. et al., (2004) "New Secondary Metabolites of Phenylbutyrate in Humans and Rats," *Drug Metabolism and Disposition* 32(1):10-19.
Lee, B. et al. (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))." *J Inherited Metabolic Disease* 31(1):91.
Lee, B. et al. (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.
Lee, B. et al. (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. (2009) "Phase 2 Study of a Novel Ammonia Scavenging Agent in Adults With Urea Cycle Disorders (UCDs)," abstract presented at ACMG 2009, one page.
Lee, B. et al. (2009) "Phase 2 Study of a Novel Ammonia Scavenging Agent in Adults with Urea Cycle Disorders (UCDs)," presented at ACMG 2009, seventeen pages.
Lee, B., 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* 100:221-228.
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.
Liang, K.Y., et al., (1986) "Longitudinal Data Analysis Using Generalized Linear Models," *Biometrika* 73(1):13-22.
Lichter-Konecki, U., et al., "Ammonia Control in Children with Urea Cycle Disorders (UCDs); Phase 2 Comparison of Sodium Phenyl butyrate and Glycerol Phenylbutyrate," *Mol Genet Metab* 103:323-329 (2011).

(56) **References Cited**

OTHER PUBLICATIONS

administrtion as both a bolus and continuous infusion to healthy adult volunteers." *Mol Genet Metab* 81:(1):S67-S73 (2004).
Maestri, N. E. et al. "Plasma Glutamine Concentration: A Guide in the Management of Urea Cycle Disorders," *J Pediatr* 121(2):259-261(Aug. 1992).
Mansour, A. et al. "Abdominal Operations in Patients with Cirrhosis: Still a Major Surgical Challenge," *Surgery* 122(4):730-735. (Abstract Only.) (Oct. 1997).
McGuire, B. et al. (2008) "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.
McGuire, B. et al. (2008) Pharmacokinetic Safety Study of Sodium Phenylacetate and Sodium Benzoate Administered to Subjects With Hepatic Impairments, *Liver International* 28:743. (Abstract Only).
McGuire, B. 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.
McGuire, B. et al. (2009) "Pharmacokinetic (PK) and Safety Analyses of a Novel Ammonia-Reducing Agent in Healthy Adults and Patients with Cirrhosis," abstract presented at DDW, two pages.
McGuire, B. et al., (2010) "Pharmacology and Safety of Glycerol Phenylbutyrate in Healthy Adults and Adults with Cirrhosis," *Hepatology* 51:2077-2085.
McQuade P.S. (1984) "Analysis and the Effects of Some Drugs on the Metabolism of Phenylethylamine and Phenylacetic Acid," *Neuropsychopharmaco Biol Psychiat* 8:607-614.
Mercuri, E., et al., (2004) "Pilot Trial of Phenylbutyrate in Spinal Muscular Atrophy," *Neuromuscul Disord* 14:130-135.
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.
Moldave, K., et al., (1957) "Synthesis of Phenylacetylglutamine by Human Tissue," *J Biol Chem* 229:463-476.
Monteleone, JPR, et al., (2012) "Population pk Analysis of Glycerol Phenylbutyrate (GPB) and Sodium Phenylbutyrate(NAPBA) in Adult and Pediatric Patients with Urea Cycle Disorders," *Mol Genet Metab* 105:343.
Ong, J. P., et al., (2003) "Correlation Between Ammonia Levels and the Severity of Hepatic Encephalopathy," *Am J Med* 114:188-193.
Perrine, S. P., (2008) "Fetal Globin Stimulant Therapies in the Beta-Hemoglobinopathies: Principles and Current Potential," *Pediatr Ann* 37(5):339-346.
Piscitelli, S.C. et al. (1995) "Disposition of Phenylbutyrate and its Metabolites, Phenylacetete and Phenylacetylglutamine," *J Clin Pharmacal* 35:368-373.
Propst, A. et al. (1995) "Prognosis and Life Expectancy in Chronic Liver Disease," *Dig Dis Sci* 40(8):1805-1815. (Abstract Only).
Riley, T.R. et al. (2001) "Preventive Strategies in Chronic Liver Disease: Part II. Cirrhoses," *Am Fam Physician* 64(10):1735-1740. (Abstract Only).
Rudman, D., et al., (1973) "Maximal Rates of Excretion and Synthesis of Urea in Normal and Cirrhotic Subjects," *J Clin Invest* 52:2241-2249.
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.
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.
Simell, O., et al. (1986) "Waste nitrogen excretion via amino acid acylation: Benzoate and phyylacetate in lysinuric protein intolerance." *Ped Res* 20(11):1117-1121.
Singh, (2001) "Consensus Statement from a Conference for the
Stauch, et al., (1998) "Oral L-ornithine-L-aspartate therapy of chronic hepatic encephalopathy: results of a placebo-controlled double-blind study" *J Hepatology* 28(5):856-864.
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, Sep. 4-7, 2007, GSSIEM 2007, two pages.
Summar, M.L. et al. "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 (Oct. 2008, e-pub. Jul. 17, 2008).
Swedish Orphan International, "Urea Cycle Disorders an International Perspective," Poster, Symposium Swedish Orphan International, Barcelona, Spain, Jan. 12, 2007, one page.
Tanner, L. M., et al., (2007) "Nutrient intake in lysinuric protein intolerance." *J Inherited Metabolic Disease* 30(5):716-721.
Thibault, A. et al., (1994) "A Phase I and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer," *Cancer Res* 54(7):1690-1694.
Thibault, A., et al., (1995) "Phase I Study of Phenylacetate Administered Twice Daily to Patients with Cancer," *Cancer* 75(12):2932-2938.
Tuchman, M. et al. (2008) "Cross-Sectional Multicenter Study of Patients With Urea Cycle Disorders in the United States," *Malec Genetics Metab* 94:397-402 (e-pub. Jun. 17, 2008).
Waterlow, J.C. (1963) "The Partition of Nitrogen in the Urine of Malnourished Jamaican Infants," *Am J Clin Nutrition* 12:235-240.
Xie, G., et al., (2012) "Role of Differentiation of Liver Sinusoidal Endothelial Cells in Progression and Regression of Hepatic Fibrosis in Rats," *Gastroenterology* 142:S918.
Zeitlin, P.L. et al. (2002) "Evidence of CFTR Function in Cystic Fibrosis After System Administration of 4-Phenylbutyrate," *Mol Therapy* 6(1):119-126.
Combined Search and Examination Report for British Patent Application No. GB0915545.8, search completed Oct. 8, 2009, report dated Oct. 9, 2009.
Combined Search and Examination Report for British Patent Application No. GB1013468.2, search completed Sep. 8, 2010, report dated Sep. 9, 2010.
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 for British Patent Application No. GB0915545.8 dated Feb. 5, 2010.
Examination Report for British Patent Application No. GB0915545.8 dated May 11, 2010.
Examination Report for British Patent Application No. GB0915545.8 dated Oct. 27, 2010.
Examination Report for British Patent Application No. GB1013468.2 dated Oct. 28, 2011.
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.
International Preliminary Report on Patentability for PCT/US2009/030362, completed Feb. 24, 2009 and mailed on Mar. 10, 2011.
International Preliminary Report on Patentability for PCT/US2009/055256, completed on Aug. 27, 2009, mailed on Mar. 10, 2011.
United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2009/030362 mailed Mar. 2, 2009.
United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2012/028620 mailed Jun. 20, 2012.
United States Patent and Trademark Office, International Search

(56) **References Cited**

OTHER PUBLICATIONS

United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2013/71333 mailed Mar. 28, 2014.
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.
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, et al., Treatment of Carbamyl Phosphate Synthetase Deficiency with Keto Analogues of Essential Amino Acids, 292 The New England J. Medicine, 1085□90 (1975).
Batshaw, M. L. et. al., Alternative Pathway Therapy for Urea Cycle Disorder: Twenty Years Later, 138 J. Pediatrics S46 (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).
Burlina, A.B. et al., Long-Term Treatment with Sodium Phenylbutyrate in Ornithine Transcarbamylase-Deficient Patients, 72 Molecular Genetics and Metabolism 351-355 (2001).
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).
Chen, Z. et al., Tributyrin: A Prodrug of Butyric Acid for Potential Clinical Application in Differentiation Therapy, 54 Cancer Research 3494 (1994).
Clay, A. et. al, Hyperammonemia in the ICU, 132 Chest 1368 (2007).
Collins, A.F. et al., Oral Sodium Phenylbutyrate Therapy in Homozygous Beta Thalassemia: A Clinical Trial, 85 Blood 43 (1995).
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).
Darmaun, D. et al., Phenylbutyrate-Induced Glutamine Depletion in Humans: Effect on Leucine Metabolism, 5 Am. J. of Physiology: Endocrinology and Metabolism E801 (1998).
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
Endo, F. et al., Clinical Manifestations of Inborn Errors of the Urea Cycle and Related Metabolic Disorders During Childhood, 134 J. Nutrition 1605S (2004).
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).
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).
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 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).
Gropman, A.L. et al., Neurological Implications of Urea Cycle Disorders, 30 J. Inherit Metab Dis. 865 (2007).
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).
Honda, S. et al., Successful Treatment of Severe Hyperammonemia Using Sodium Phenylacetate Power Prepared in Hospital Pharmacy, 25 Biol. Pharm. Bull. 1244 (2002).
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.
Inter Partes Review of U.S. Pat. No. 8,404,215 Petition Apr. 29, 2015.
Inter Partes Review of U.S. Pat. No. 8,642,012 Petition Apr. 29, 2015.
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).
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., "Optimizing Ammonia (NH3) Control in Urea Cycle Disorder (UCD) Patients: A Predictive Model," Oral Abstract Plat-

(56) **References Cited**

OTHER PUBLICATIONS

Leonard, J.V., Urea Cycle Disorders, 7 Semin. Nenatol. 27 (2002).
Lizardi-Cervera, J. et al., Hepatic Encephalopathy: A Review, 2 Annals of Hepatology 122-120 (2003).
Maestri NE, et al., Prospective treatment of urea cycle disorders. J Paediatr 1991;119:923-928.
Maestri, N.E., et al., Long-Term Survival of Patients with Argininosuccinate Synthetase Deficiency, 127 J. Pediatrics 929 (1995).
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).
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).
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., (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, 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., (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).
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).
Phuphanich, S. et al., Oral Sodium Phenylbutyrate in Patients with Recurrent Malignant Gliomas: A Dose Escalation and Pharmacologic Study, Neuro-Oncology 177 (2005).
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).
Rockey, D. C., et al., "Randomized, Controlled, Double Blind Study
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.
Scottish Medicines Consortium, Carglumic Acid 200 mg Dispersible Tablets (Carbaglu®) No. 299/06 (Sep. 8, 2006).
Seakins, J.W.T., The Determination of Urinary Phenylacetylglutamine as Phenylacetic Acid: Studies on its Origin in Normal Subjects and Children with Cystic Fibrosis, 35 Clin. Chim. Acta.121 (1971).
Sherwin, C. et al., The Maximum Production of Glutamine by the Human Body as Measured by the Output of Phenylacetylglutamine, 37 J. Biol. Chem. 113 (1919).
Smith, W., et al., "Ammonia Control in Children Ages 2 Months through 5 Years with Urea Cycle Disorders: Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate," J Pediatr. 162(6):1228-1234.e1 (2013).
Summar, M., Current Strategies for the Management of Neonatal Urea Cycle Disorders, 138 J. Pediatrics S30 (2001).
Summar, M. and Tuchman, M., Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders, 138 J. Pediatrics S6 (2001).
Summar, M., Urea Cycle Disorders Overview, Gene Reviews, www.genetests.org (Apr. 2003).
Summar, M. et al., Unmasked Adult-Onset Urea Cycle Disorders in the Critical Care Setting, 21 Crit. Care Clin. S1 (2005).
The National Organization for Rare Disorders (2012). The Physician's Guide to Urea Cycle Disorders, at http://nordphysicianguides.org/wp-content/uploads/2012/02/NORD_Physician_Guide_to_Urea_Cycle_Disorders.pdf.
Todo, S. et al., Orthotopic Liver Transplantation for Urea Cycle Enzyme Deficiency, 15 Hepatology 419 (1992).
Tuchman, M., and Yudkoff, M., Blood Levels of Ammonia and Nitrogen Scavenging Amino Acids in Patients with Inherited Hyperammonemia, 66 Molecular Genetics and Metabolism 10-15 (1999).
United States Patent and Trademark Office, International Search Report and Written Opinion dated Jan. 16, 2015 for PCT/US14/58489.
United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2014/060543 dated Jan. 23, 2015.
Vilstrup, H., et al., "Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver," Hepatology 60 (2):715-735 (2014).
Walsh et al., Chemical Abstract vol. 112, No. 231744.
Welbourne, T. et al., The Effect of Glutamine Administration on Urinary Ammonium Excretion in Normal Subjects and Patients with Renal Disease, 51 J. Clin. Investigation 1852 (1972).
Wilcken, B., Problems in the Management of Urea Cycle Disorders, 81 Molecular Genetics and Metabolism 85 (2004).
Wilson, C.J., et al., Plasma Glutamine and Ammonia Concentrations in Ornithine Carbamoyltransferase Deficiency and Citrullinaemia, 24 J. Inherited Metabolic Disease 691 (2001).
Wright, G., et al., Management of Hepatic Encephalopathy, 2011 International Journal of Hepatology 1 (2011).
Wright, P., Review: Nitrogen Excretion: Three End Products, Many Physiological Roles, 198 J. Experimental Biology 273 (1995).
Yajima, et al. Diurnal Fluctuations of Blood Ammonia Levels in Adult-Type Citrullinemia, 137 Tokohu J. Ex/ Med, 213-220 (1982).
Yu, Ryan and Potter, Murray, Diagnosis of Urea Cycle Disorders in Adulthood: Late-Onset Carbamyl Phosphate Synthetase 1 Deficiency, 7 MUMJ 30 (2010).
Yudkoff, M. et al., In Vivo Nitrogen Metabolism in Ornithine Transcarbamylase Deficiency, 98 J. Clin. Invest. 2167 (1996).
Zeitlin, P., Novel Pharmacologic Therapies for Cystic Fibrosis, 103 J. Clinical Investigation 447 (1999).
Ahrens, M. et al. (Jan. 2001). "Consensus Statement From a

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.