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NEW APPLICATION TRANSMITTAL - UTILITY

Sir:

Transmitted herewith for filing is a utility patent application:

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Masoud MOKHTARANI

Title: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

I. PAPERS ENCLOSED HEREWITH FOR FILING UNDER 37 CFR § 1.53(b):

41 Page(s) of Written Description
3 Page(s) Claims
1 Page(s) Abstract
7 Sheets of Drawings
Sheets of Sequence Listing

II. ADDITIONAL PAPERS ENCLOSED IN CONNECTION WITH THIS FILING:

- ☐ Declaration
- ☐ Power of Attorney ☐ Separate ☐ Combined with Declaration
- ☐ Assignment to and assignment cover sheet
- ☐ Certified Copy of Priority Document No(s): _____
- ☐ Information Disclosure Statement w/PTO 1449 ☐ Copy of Citations
- ☐ Preliminary Amendment
- ☐ Sequence Listing Diskette and Declaration
- ☐ Request and Certification under 35 U.S.C. § 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35
- ☐ Return Postcard

III. U.S. PRIORITY:

The present application claims priority to U.S. Provisional Application No. 61/636,256, filed April 20, 2012, the disclosure of which is incorporated by reference herein in its entirety, including drawings.

IV. FEES:

☒ Applicant claims small entity status pursuant to 37 CFR § 1.27
☒ This application is being filed without fee or Declaration under 37 CFR § 1.53.

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Respectfully submitted,

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METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Application No. 61/636,256, filed April 20, 2012, the disclosure of which is incorporated by reference herein in its entirety, including drawings.

BACKGROUND

[0002] Nitrogen retention disorders associated with elevated ammonia levels include urea cycle disorders (UCDs), hepatic encephalopathy (HE), and advanced kidney disease or kidney failure, often referred to as end-stage renal disease (ESRD).

[0003] UCDs include several inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia, including enzymes involved in the urea cycle. The urea cycle is depicted in Figure 1, which also illustrates how certain ammonia-scavenging drugs act to assist in elimination of excessive ammonia. With reference to Figure 1, N-acetyl glutamine synthetase (NAGS)-derived *N*-acetylglutamate binds to carbamyl phosphate synthetase (CPS), which activates CPS and results in the conversion of ammonia and bicarbonate to carbamyl phosphate. In turn, carbamyl phosphate reacts with ornithine to produce citrulline in a reaction mediated by ornithine transcarbamylase (OTC). A second molecule of waste nitrogen is incorporated into the urea cycle in the next reaction, mediated by arginosuccinate synthetase (ASS), in which citrulline is condensed with aspartic acid to form argininosuccinic acid. Argininosuccinic acid is cleaved by argininosuccinic lyase (ASL) to produce arginine and fumarate. In the final reaction of the urea cycle, arginase (ARG) cleaves arginine to produce ornithine and urea. Of the two atoms of nitrogen incorporated into urea, one originates from free ammonia (NH_4^+) and the other from aspartate. UCD individuals born with no meaningful residual urea synthetic capacity typically present in the first few days of life (neonatal presentation). Individuals with residual function typically present later in childhood or even in adulthood, and symptoms may be precipitated by increased dietary protein or physiological stress (e.g., intercurrent illness). For UCD patients, lowering blood ammonia is the cornerstone of treatment.

[0004] HE refers to a spectrum of neurologic signs and symptoms believed to result from hyperammonemia, which frequently occur in subjects with cirrhosis or certain other types of liver

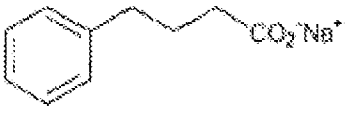
disease. HE is a common manifestation of clinically decompensated liver disease and most commonly results from liver cirrhosis with diverse etiologies that include excessive alcohol use, hepatitis B or C virus infection, autoimmune liver disease, or chronic cholestatic disorders such as primary biliary cirrhosis. Patients with HE typically show altered mental status ranging from subtle changes to coma, features similar to patients with UCDs. It is believed that an increase in blood ammonia due to dysfunctional liver in detoxifying dietary protein is the main pathophysiology associated with HE (Ong 2003).

[0005] ESRD results from a variety of causes including diabetes, hypertension, and hereditary disorders. ESRD is manifested by accumulation in the bloodstream of substances normally excreted in the urine, including but not limited to urea and creatinine. This accumulation in the bloodstream of substances, including toxins, normally excreted in the urine is generally believed to result in the clinical manifestations of ESRD, sometimes referred to also as uremia or uremic syndrome. ESRD is ordinarily treated by dialysis or kidney transplantation. To the extent that urea, per se, contributes to these manifestations and that administration of a phenylacetic (PAA) prodrug may decrease synthesis of urea (see, e.g., Brusilow 1993) and hence lower blood urea concentration, PAA prodrug administration may be beneficial for patients with ESRD.

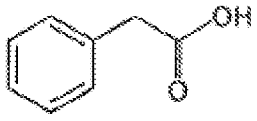
[0006] Subjects with nitrogen retention disorders whose ammonia levels and/or symptoms are not adequately controlled by dietary restriction of protein and/or dietary supplements are generally treated with nitrogen scavenging agents such as sodium phenylbutyrate (NaPBA, approved in the United States as BUPHENYL® and in Europe as AMMONAPS®), sodium benzoate, or a combination of sodium phenylacetate and sodium benzoate (AMMONUL®). These are often referred to as alternate pathway drugs because they provide the body with an alternate pathway to urea for excretion of waste nitrogen (Brusilow 1980; Brusilow 1991). NaPBA is a PAA prodrug. Another nitrogen scavenging drug currently in development for the treatment of nitrogen retention disorders is glyceryl tri-[4-phenylbutyrate] (HPN-100), which is described in U.S. Patent No. 5,968,979. HPN-100, which is commonly referred to as GT4P or glycerol PBA, is a prodrug of PBA and a pre-prodrug of PAA. The difference between HPN-100 and NaPBA with respect to metabolism is that HPN-100 is a triglyceride and requires digestion, presumably by pancreatic

lipases, to release PBA (McGuire 2010), while NaPBA is a salt and is readily hydrolyzed after absorption to release PBA.

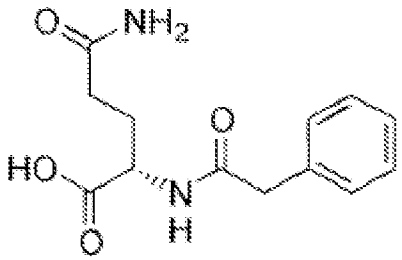
[0007] HPN-100 and NaPBA share the same general mechanism of action: PBA is converted to PAA via beta oxidation, and PAA is conjugated enzymatically with glutamine to form phenylacetylglutamine (PAGN), which is excreted in the urine. The structures of PBA, PAA, and PAGN are set forth below:



phenylbutyrate



Phenylacetic acid



Phenylacetylglutamine

[0008] The clinical benefit of NaPBA and HPN-100 with regard to nitrogen retention disorders derives from the ability of PAGN to effectively replace urea as a vehicle for waste nitrogen excretion and/or to reduce the need for urea synthesis (Brusilow 1991; Brusilow 1993). Because each glutamine contains two molecules of nitrogen, the body rids itself of two waste nitrogen atoms for every molecule of PAGN excreted in the urine. Therefore, two equivalents of nitrogen are removed for each mole of PAA converted to PAGN. PAGN represents the predominant terminal metabolite, and one that is stoichiometrically related to waste nitrogen removal, a measure of efficacy in the case of nitrogen retention states.

[0009] In addition to nitrogen retention states, PAA prodrugs may be beneficial in a variety of other disorders for which PBA and/or PAA are believed to modify gene expression and/or exert post-translational effects on protein function. In the case of maple syrup urine disease (MSUD, also

known as branched-chain ketoaciduria), for example, the apparently beneficial effect of NaPBA in lowering plasma levels of branched chain amino acids is reported to be mediated by PBA-induced inhibition of the kinase that regulates activity of branched chain alpha-keto acid dehydrogenase complex or BCKDC. BCKDC is the enzyme that normally breaks down branched-chain amino acids and is genetically defective in MSUD patients (Bruneti-Pieri 2011). Similarly, the putative beneficial effects of PAA prodrugs for the treatment of cancer (Chung 2000), neurodegenerative diseases (Ryu 2005), and sickle cell disease (Perrine 2008) all involve alteration of gene expression and/or post-translational effects on protein function via PBA and/or PAA.

[0010] Numerous publications reports adverse events following administration of PBA and/or PAA (Mokhtarani 2012), and PAA is reported to cause reversible toxicity when present in high levels in circulation. While many of these publications have not recorded PAA blood levels and/or temporally correlated adverse events with PAA levels, toxicities such as nausea, headache, emesis, fatigue, weakness, lethargy, somnolence, dizziness, slurred speech, memory loss, confusion, and disorientation have been shown to be temporally associated with PAA levels ranging from 499–1285 μg/mL in cancer patients receiving PAA intravenously, and these toxicities have been shown to resolve with discontinuation of PAA administration (Thiebault 1994; Thiebault 1995). Therefore, when administering PAA prodrugs for treatment of nitrogen retention disorders and other conditions, it is important to optimize dosing so as to achieve the desired therapeutic effect while minimizing the risk of PAA associated toxicity.

SUMMARY

[0011] Provided herein is a clinically practical approach for utilizing and interpreting blood levels of PAA and PAGN to adjust the dose of a PAA prodrug in order to minimize the risk of toxicities and maximize drug effectiveness.

[0012] Provided herein in certain embodiments are methods of treating a nitrogen retention disorder or a condition for which PAA prodrug administration is expected to be beneficial in a subject comprising the steps of administering a first dosage of a PAA prodrug, measuring plasma PAA and PAGN levels, calculating a plasma PAA:PAGN ratio, and determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range. In certain embodiments, the target range is 1 to 2.5, 1 to 2, 1 to 1.5, 1.5 to 2, or 1.5 to 2.5. In

certain embodiments, a PAA:PAGN ratio above the target range indicates that the dosage of the PAA prodrug needs to be decreased. In other embodiments, a PAA:PAGN ratio above the target range indicates that the dosage may need to be decreased, with the final determination of whether to decrease the dosage taking into account other characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. In certain embodiments, a PAA:PAGN ratio below the target range indicates that the dosage of the PAA prodrug needs to be increased. In other embodiments, a PAA:PAGN ratio below the target range indicates that the dosage may need to be increased, with the final determination of whether to increase the dosage taking into account other characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. In certain embodiments, a PAA:PAGN ratio that is within the target range but within a particular subrange (e.g., 1 to 1.5 or 2 to 2.5 where the target range is 1 to 2.5) indicates that the dosage of the PAA prodrug does not need to be adjusted, but that the subject needs to be subjected to more frequent monitoring. In certain embodiments, the methods further comprise a step of administering an adjusted second dosage if such an adjustment is determined to be necessary based on the PAA:PAGN ratio and, optionally, other characteristics of the subject. In other embodiments, the methods further comprise a step of administering a second dosage that is the same as or nearly the same as the first dosage if no adjustment in dosage is deemed to be necessary. In certain embodiments, the nitrogen retention disorder is UCD, HE, or ESRD. In certain embodiments, the condition for which PAA prodrug administration is expected to be beneficial is cancer, a neurodegenerative diseases, a metabolic disorder, or sickle cell disease. In certain embodiments, the PAA prodrug is HPN-100 or NaPBA. In certain embodiments, measurement of plasma PAA and PAGN levels takes place after the first dosage of the PAA prodrug has had sufficient time to reach steady state, such as at 48 hours to 1 week after administration.

[0013] Provided herein in certain embodiments are methods of treating a nitrogen retention disorder or a condition for which PAA prodrug administration is expected to be beneficial in a subject who has previously received a first dosage of PAA prodrug comprising the steps of measuring plasma PAA and PAGN levels, calculating a plasma PAA:PAGN ratio, and determining

whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range. In certain embodiments, the target range is 1 to 2.5, 1 to 2, 1 to 1.5, 1.5 to 2, or 1.5 to 2.5. In certain embodiments, a PAA:PAGN ratio above the target range indicates that the dosage of the PAA prodrug needs to be decreased. In other embodiments, a PAA:PAGN ratio above the target range indicates that the dosage may need to be decreased, with the final determination of whether to decrease the dosage taking into account other characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. In certain embodiments, a PAA:PAGN ratio below the target range indicates that the dosage of the PAA prodrug needs to be increased. In other embodiments, a PAA:PAGN ratio below the target range indicates that the dosage may need to be increased, with the final determination of whether to increase the dosage taking into account other characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. In certain embodiments, a PAA:PAGN ratio that is within the target range but within a particular subrange (e.g., 1 to 1.5 or 2 to 2.5 where the target range is 1 to 2.5) indicates that the dosage of the PAA prodrug does not need to be adjusted, but that the subject needs to be subjected to more frequent monitoring. In certain embodiments, the methods further comprise a step of administering an adjusted second dosage if such an adjustment is determined to be necessary based on the PAA:PAGN ratio and, optionally, other characteristics of the subject. In other embodiments, the methods further comprise a step of administering a second dosage that is the same as or nearly the same as the first dosage if no adjustment in dosage is deemed to be necessary. In certain embodiments, the nitrogen retention disorder is UCD, HE, or ESRD. In certain embodiments, the condition for which PAA prodrug administration is expected to be beneficial is cancer, a neurodegenerative diseases, a metabolic disorder, or sickle cell disease. In certain embodiments, measurement of plasma PAA and PAGN levels takes place after the first dosage of the PAA prodrug has had sufficient time to reach steady state, such as at 48 hours to 1 week after administration.

[0014] Provided herein in certain embodiments are methods of adjusting the dosage of a PAA prodrug to be administered to a subject comprising the steps of administering a first dosage of a

PAA prodrug, measuring plasma PAA and PAGN levels, calculating a plasma PAA:PAGN ratio, and determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range. In certain embodiments, the target range is 1 to 2.5, 1 to 2, 1 to 1.5, 1.5 to 2, or 1.5 to 2.5. In certain embodiments, a PAA:PAGN ratio above the target range indicates that the dosage of the PAA prodrug needs to be decreased. In other embodiments, a PAA:PAGN ratio above the target range indicates that the dosage may need to be decreased, with the final determination of whether to decrease the dosage taking into account other characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. In certain embodiments, a PAA:PAGN ratio below the target range indicates that the dosage of the PAA prodrug needs to be increased. In other embodiments, a PAA:PAGN ratio below the target range indicates that the dosage may need to be increased, with the final determination of whether to increase the dosage taking into account other characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. In certain embodiments, a PAA:PAGN ratio that is within the target range but within a particular subrange (e.g., 1 to 1.5 or 2 to 2.5 where the target range is 1 to 2.5) indicates that the dosage of the PAA prodrug does not need to be adjusted, but that the subject needs to be subjected to more frequent monitoring. In certain embodiments, the methods further comprise a step of administering an adjusted second dosage if such an adjustment is determined to be necessary based on the PAA:PAGN ratio and, optionally, other characteristics of the subject. In other embodiments, the methods further comprise a step of administering a second dosage that is the same as or nearly the same as the first dosage if no adjustment in dosage is deemed to be necessary. In certain embodiments, measurement of plasma PAA and PAGN levels takes place after the first dosage of the PAA prodrug has had sufficient time to reach steady state, such as at 48 hours to 1 week after administration.

[0015] Provided herein in certain embodiments are methods of determining whether a first dosage of a PAA prodrug can be safely administered to a subject comprising the steps of administering the first dosage of a PAA prodrug, measuring plasma PAA and PAGN levels, calculating a plasma PAA:PAGN ratio, and determining whether the first dosage can be safely

administered based on whether the PAA:PAGN ratio falls above a target range. In certain embodiments, the target range is 1 to 2.5, 1 to 2, 1 to 1.5, 1.5 to 2, or 1.5 to 2.5. In certain embodiments, a PAA:PAGN ratio above the target range indicates that the first dosage is unsafe and needs to be decreased. In other embodiments, a PAA:PAGN ratio above the target range indicates that the first dosage is potentially unsafe and may need to be decreased, with the final determination of whether to decrease the dosage taking into account other characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. In certain embodiments, a PAA:PAGN ratio that is within the target range but within a particular subrange (e.g., 2 to 2.5 where the target range is 1 to 2.5) indicates that the first dosage is likely safe, but that the subject needs to be subjected to more frequent monitoring. In certain embodiments, the methods further comprise a step of administering an adjusted second dosage if such an adjustment is determined to be necessary based on the PAA:PAGN ratio and, optionally, other characteristics of the subject. In certain embodiments, measurement of plasma PAA and PAGN levels takes place after the first dosage of the PAA prodrug has had sufficient time to reach steady state, such as at 48 hours to 1 week after administration.

[0016] Provided herein in certain embodiments are methods of determining whether a first dosage of a PAA prodrug is likely to be effective for treating a nitrogen retention disorder or another disorder for which PAA prodrug administration is expected to be beneficial comprising the steps of administering the first dosage of a PAA prodrug, measuring plasma PAA and PAGN levels, calculating a plasma PAA:PAGN ratio, and determining whether the first dosage is likely to be effective based on whether the PAA:PAGN ratio falls below a target range. In certain embodiments, the target range is 1 to 2.5, 1 to 2, 1 to 1.5, 1.5 to 2, or 1.5 to 2.5. In certain embodiments, a PAA:PAGN ratio below the target range indicates that the first dosage is unlikely to be effective needs to be increased. In other embodiments, a PAA:PAGN ratio below the target range indicates that the first dosage is potentially ineffective and may need to be increased, with the final determination of whether to increase the dosage taking into account other characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. In certain

embodiments, a PAA:PAGN ratio that is within the target range but within a particular subrange (e.g., 1 to 1.5 where the target range is 1 to 2.5) indicates that the first dosage is likely effective, but that the subject needs to be subjected to more frequent monitoring. In certain embodiments, the methods further comprise a step of administering an adjusted second dosage if such an adjustment is determined to be necessary based on the PAA:PAGN ratio and, optionally, other characteristics of the subject. In certain embodiments, measurement of plasma PAA and PAGN levels takes place after the first dosage of the PAA prodrug has had sufficient time to reach steady state, such as at 48 hours to 1 week after administration.

[0017] In certain embodiments, methods are provided for optimizing the therapeutic efficacy of a PAA prodrug in a subject who has previously been adminsitered a first dosage of PAA prodrug comprising the steps of measuring plasma PAA and PAGN levels, calculating a plasma PAA:PAGN ratio, and determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range. In certain embodiments, the target range is 1 to 2.5, 1 to 2, 1 to 1.5, 1.5 to 2, or 1.5 to 2.5. In certain embodiments, a PAA:PAGN ratio above the target range indicates that the dosage of the PAA prodrug needs to be decreased. In other embodiments, a PAA:PAGN ratio above the target range indicates that the dosage may need to be decreased, with the final determination of whether to decrease the dosage taking into account other characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. In certain embodiments, a PAA:PAGN ratio below the target range indicates that the dosage of the PAA prodrug needs to be increased. In other embodiments, a PAA:PAGN ratio below the target range indicates that the dosage may need to be increased, with the final determination of whether to increase the dosage taking into account other characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. In certain embodiments, a PAA:PAGN ratio that is within the target range but within a particular subrange (e.g., 1 to 1.5 or 2 to 2.5 where the target range is 1 to 2.5) indicates that the dosage of the PAA prodrug does not need to be adjusted, but that the subject needs to be subjected to more frequent monitoring. In certain embodiments, the methods further comprise a step of administering an adjusted second dosage if

such an adjustment is determined to be necessary based on the PAA:PAGN ratio and, optionally, other characteristics of the subject. In other embodiments, the methods further comprise a step of administering a second dosage that is the same as or nearly the same as the first dosage if no adjustment in dosage is deemed to be necessary. In certain embodiments, measurement of plasma PAA and PAGN levels takes place after the first dosage of the PAA prodrug has had sufficient time to reach steady state, such as at 48 hours to 1 week after administration.

[0018] In certain embodiments, methods are provided for obtaining a plasma PAA:PAGN ratio within a target range in a subject comprising the steps of administering a first dosage of a PAA prodrug, measuring plasma PAA and PAGN levels, calculating a plasma PAA:PAGN ratio, and determining whether the PAA:PAGN ratio falls within the target range. If the PAA:PAGN ratio does not fall within the target range, an adjusted second dosage is administered, and these steps are repeated until a plasma PAA:PAGN ratio falling within the target range is achieved. In certain embodiments, the target range is 1 to 2.5, 1 to 2, 1 to 1.5, 1.5 to 2, or 1.5 to 2.5. In certain embodiments, a PAA:PAGN ratio above the target range indicates that the dosage of the PAA prodrug needs to be decreased and a PAA:PAGN ratio below the target range indicates that the dosage of the PAA prodrug needs to be increased. In certain embodiments, measurement of plasma PAA and PAGN levels takes place after the first dosage of the PAA prodrug has had sufficient time to reach steady state, such as at 48 hours to 1 week after administration.

BRIEF DESCRIPTION OF DRAWINGS

[0019] Figure 1: Urea cycle.

[0020] Figure 2: Plasma PAA levels versus plasma PAA:PAGN ratio in (A) all subjects combined (healthy adults, patients age 2 months and above with UCDs, and patients with cirrhosis), (B) patients age 2 months and above with UCDs, and (C) patients with cirrhosis.

[0021] Figure 3: Estimated probability (95% confidence interval (c.i.)) of correctly detecting elevated plasma PAA:PAGN ratio (≥2.0) with a single blood sample at a designated time.

[0022] Figure 4:Distribution of plasma PAA:PAGN ratio (log scale) by time since dosing (hours) and category of maximum PAA:PAGN ratio in all subjects combined.

[0023] Figure 5: Distribution of plasma PAA concentrations (μg/mL) by PAA:PAGN ratio for (A) all subjects and (B) UCD and HE subjects.

DETAILED DESCRIPTION

[0024] The following description of the invention is merely intended to illustrate various embodiments of the invention. As such, the specific modifications discussed are not to be construed as limitations on the scope of the invention. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of the invention, and it is understood that such equivalent embodiments are to be included herein.

[0025] The enzymes responsible for beta oxidation of PBA to PAA are present in most cell types capable of utilizing fatty acids as energy substrates, and the widespread distribution of these enzymes presumably accounts for the rapid and essentially complete conversion of PBA to PAA. However, the enzymes that conjugate PAA with glutamine to form PAGN are found primarily in the liver and to a lesser extend in kidneys (Moldave 1957). Therefore, the conversion of PAA to PAGN may be affected under several circumstances, including the following: a) if conjugation capacity is saturated (e.g., by high doses of PAA prodrug); b) if conjugation capacity is compromised (e.g., by severe hepatic and/or renal dysfunction); c) if the substrate (glutamine) for PAA to PAGN conjugation is rate limiting; d) genetically determined variability (i.e., polymorphisms) in the enzymes responsible for PAA to PAGN conversion, or e) in young children, since the capacity to convert PAA to PAGN varies with body size measured as body surface area (Monteleone 2012). The presence of any one of these conditions may lead to accumulation of PAA in the body, which causes reversible toxicity.

[0026] The goal of PAA prodrug administration in subjects with nitrogen retention disorders is to provide a sufficient dosage to obtain a desired level of nitrogen removal while avoiding excess build-up of PAA. The goal of PAA prodrug administration in patients without a nitrogen retention disorder (e.g., a neurodegenerative disease) is to achieve circulating metabolite levels necessary to produce a clinical benefit by alteration of gene expression and/or protein folding or function. However, there are several difficulties associated with determining the proper dosage in patients with nitrogen retention disorders.

[0027] Plasma PAA and PAGN levels are affected by various factors, including timing of the blood draw in relation to drug administration, hepatic function, availability of metabolizing enzymes, and availability of substrates required for metabolism. A random PAA level drawn during

an outpatient visit to determine if levels are in the toxicity range without considering concomitant PAGN level is insufficient to inform dosing. First, PAA levels vary many-fold over the course of the day, fluctuating a great deal between peak and trough levels. For example, in the Hyperion pivotal study evaluating HPN-100 for use in treating adult UCD (Study ID HPN-100-006, Clinical Trials ID NCT00992459), serial blood samples were obtained for PK studies over a 24 hour period during which subjects were receiving HPN-100 or NaPBA. The fluctuation index for PAA over a 24 hour period, which represents the fluctuation between maximum concentration (typically observed after the last daily dose or at approximately 12 hours) and minimum concentration (typically observed in the morning after overnight fasting or at 0 hours), indicated a very high degree of variability (2150% for NaPBA and 1368% for HPN-100). Therefore, a single plasma PAA level may not be representative of the highest PAA level a patient may experience during the day. Second, a high plasma PAA level may only be indicative of the high doses a subject is receiving rather than a point of concern if the subject is effectively conjugating PAA with glutamine to form PAGN. Therefore, basing dose adjustment on only on a high PAA level without considering concomitant plasma PAGN level may result in unnecessary dose reduction and under-treatment of the patient. Conversely, a PAA level seemingly below the levels associated with toxicity might be taken as an indication of satisfactory dosing without appreciating the fact that the concomitant PAGN level may not be proportional to PAA, indicating that PAA is not being efficiently utilized and may be accumulating.

[0028] Previous studies have shown that conversion of PAA to PAGN is a saturable process that varies considerably among individuals (see, e.g., Monteleone 2012), and that patients with hepatic impairment have higher PAA levels than patients without hepatic impairment (Ghabril et al., "Glycerol phenylbutyrate (GPD) administration in patients with cirrhosis and episodic hepatic encephalopathy (HE)," submitted to Digestive Disease Week, 2012). If PAGN formation is affected by any of the above factors, PAA will be accumulated and waste nitrogen may not be removed from the body. Previous studies have also shown that a small proportion of individuals, including both healthy adults ad patients with UCDs or HE, have higher PAA levels than the remainder of the population, presumably due to individual differences in conjugating PAA to PAGN, and that PAA levels fluctuate many-fold during the day depending on the dose and the timing of blood sample

relative to the last dose so that a single plasma level may not be informative (Lee 2010; Lichter 2011).

[0029] Although the goal of PAA prodrug therapy for nitrogen retention disorders is to achieve ammonia levels within a normal limit, there is no correlation between plasma PAA levels and blood ammonia. Nitrogen retention disorder subjects are normally "dosed to effect," meaning that subjects with absent or severely deficient urea synthetic capacity require higher doses of PAA prodrugs than do mildly deficient UCD patients. These higher dosages are generally associated with higher PAA levels, such that the conventional PK/PD response (higher active moiety, i.e., PAA, correlates with lower harmful substance, i.e., ammonia) does not apply. Therefore, there is no single target plasma PAA level that can be applied to patients with UCDs or other nitrogen retention disorders based on their blood ammonia.

[0030] Patients with severe hepatic impairment are at increased risk of PAA accumulation due to inadequate levels of PAA conjugating enzymes if treated with PAA-prodrugs. UCD patients without hepatic impairment whose PAA conjugating enzymes are readily saturated are also at increased risk of PAA accumulation if treated with PAA-producing compounds. Other patients without nitrogen retention are at increased risk of PAA accumulation due to limited availability of glutamine as the substrate to form PAGN if treated with PAA-producing compounds, which accumulates in patients with nitrogen retention states.

[0031] WO09/134460 and WO10/025303 disclose methods for determining an effective dosage of a PAA prodrug based on urinary PAGN levels, which was found to be a more reliable indictor of effective dosage than plasma levels of PAA or other metabolites. Although such measurements are highly useful for evaluating waste nitrogen removal, they do not provide complete information regarding a subject's ability to utilize the prodrug.

[0032] Since PAA, PAGN, and ammonia levels do not provide the information necessary to determine whether a subject is effectively converting PBA to PAGN (i.e., effectively utilizing the PAA prodrug), there is a need for improved methods of adjusting PAA prodrug dosage and incorporating such adjustments into methods of treating nitrogen retention disorders.

[0033] As disclosed herein, plasma PAA:PAGN ratio has been found to provide an unexpectedly accurate measure of PAA prodrug metabolism in subjects with nitrogen retention

disorders and/or hepatic impairment. It was found that subjects who can readily convert PAA to PAGN and have not reached the saturation point with respect to PAA to PAGN conversion will have a plasma PAA:PAGN ratio of 2.5 or below (when both are measured in μg/mL), and that subjects with PAA:PAGN ratios above 2.5 have a significantly higher chance of experience a PAA level above 400 μg/mL or 500 μg/mL over a 24 hour period. A PAA/PAGN ratio of less than 2.5 was associated primarily with healthy adult or adolescent subjects and normal liver function, with subjects having a ratio below 2.5 exhibiting a 1% probability of experiencing a PAA level greater than 400 μg/mL and almost no chance of exhibiting a PAA level greater than 500 μg/mL at any point during a 24 hour period. A ratio greater than 2.5, on the other hand, was generally seen in subjects with moderate hepatic impairment, a subset of healthy subjects or UCD patients with relatively lower saturation point and difficulty conjugating PAA to form PAGN, and patients with a low body surface area. Subjects with a ratio greater than 2.5, on the other hand, exhibited a 20-36% likelihood of experiencing a PAA level greater than 400 μg/mL during the day, and an approximately 10% likelihood of experiencing a PAA level of 500 μg/L or greater. In subjects with a ratio greater than 3, the likelihood of experiencing a PAA level higher than 500 μg/mL increased to as high as 25%. These results show that a plasma PAA:PAGN ratio exceeding 2.5 in a patient with unexplained neurological adverse events and normal ammonia indicates that dosage adjustment should be considered. Thus, plasma PAA:PAGN ratio provides a clinically useful surrogate for evaluating the efficiency of PAA to PAGN conversion.

[0034] Plasma PAA:PAGN ratio indicates whether a PAA prodrug is being effectively utilized and scavenging nitrogen, and therefore provides an indirect and simple measure of saturation of conjugating enzymes, availability of substrate, and possible effect of hepatic or renal impairment on this process. Calculating this ratio will allow effective treatment and dose adjustment in subjects with known hepatic impairment, subjects presenting with signs and symptoms overlapping between hyperammonemia and PAA toxicities, and subjects who are not clinically controlled despite increasing the dosage of drugs.

[0035] One of ordinary skill in the art would generally not consider the ratio of an active metabolite such as PAA to a terminal metabolite such as PAGN when making therapeutic decisions because they would expect that higher levels of the active metabolite would result in a

proportionately higher response (as measured by PAGN production) and increased efficacy (i.e., waste nitrogen removal). However, the results provided herein show that the use of plasma PAA:PAGN ratios to evaluate and adjust PAA prodrug dosage is unexpectedly superior to the use of PAA or PAGN levels alone. Once a subject exceeds a specific PAA:PAGN ratio, there is a high likelihood that they are not effectively utilizing the active moiety and that further increasing PAA prodrug dosage may not increase efficacy and may actually result in PAA accumulation and toxicity.

[0036] Based on these findings, methods are provided herein for treating nitrogen retention disorders and evaluating and adjusting the dosage of a PAA prodrug based on plasma PAA:PAGN ratio. Generally, these methods comprise steps of measuring plasma PAA and PAGN levels, calculating the PAA:PAGN ratio, and determining whether the ratio falls within a target range, with this determination being used at least in part to decide whether to adjust PAA prodrug dosage. In these methods, PAA:PAGN ratio can be used to ensure that urinary PAGN output, plasma ammonia concentration, and/or PAA levels fall within a predefined target range. Such methods represent an improvement over previously developed methods for evaluating PAA prodrug dosage and efficacy in that they allow for more accurate dosing, greater efficacy, and decreased risk of toxicity associated with PAA accumulation.

[0037] Disclosed herein are target ranges for the ratio of plasma PAA to PAGN in subjects who are receiving PAA prodrug therapy. In certain embodiments, a subject exhibiting a PAA:PAGN ratio falling within a target range is classified as properly dosed, meaning that they do not require a PAA prodrug dosage adjustment, while a subject exhibiting a PAA:PAGN ratio falling outside the target range is classified as improperly dosed, meaning that they require an adjustment in PAA prodrug dosage. In certain of these embodiments, a subject exhibiting a plasma PAA:PAGN ratio falling above a target range is classified as requiring a decreased dosage of PAA prodrug, while a subject exhibiting a plasma PAA:PAGN ratio falling below a target range is classified as requiring an increased dosage of PAA prodrug. In other embodiments, a subject exhibiting a plasma PAA:PAGN ratio falling above a target range is classified as requiring a decreased dosage of PAA prodrug, while a subject exhibiting a plasma PAA:PAGN ratio falling below a target range is classified as potentially requiring an increase in PAA prodrug dosage. In still other embodiments, a

subject exhibiting a plasma PAA:PAGN ratio falling above a target range is classified as potentially requiring a decreased dosage of PAA prodrug, while a subject exhibiting a plasma PAA:PAGN ratio falling below a target range is classified as potentially requiring an increase in PAA prodrug dosage. In those embodiments where a subject is classified as potentially requiring an increase or decrease in PAA prodrug dosage based on their PAA:PAGN ratio, a decision as to whether to increase or decrease dosage may be based on one or more additional characteristics of the subject such as biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health.

[0038] In certain embodiments, the target range for plasma PAA:PAGN ratio is 1 to 2.5, meaning that a subject exhibiting a PAA:PAGN falling within this range is classified as properly dosed. In other embodiments, the target range for plasma PAA:PAGN ratio is 1 to 2, 1 to 1.5, 1.5 to 2, or 1.5 to 2.5. In certain of those embodiments where the target range is 1 to 2.5, a subject with a PAA:PAGN ratio above 2.5 is classified as requiring a decrease in PAA prodrug dosage, while a subject with a PAA:PAGN ratio falling below 1 is classified as potentially requiring an increase in PAA prodrug dosage. In certain of these embodiments, a subject is necessarily classified as requiring an increase in PAA prodrug dosage if their ratio is below 1. In other embodiments, a subject with a PAA:PAGN ratio of less than 1 is only classified as requiring an increase in PAA prodrug dosage if one or more additional clinical or biochemical characteristics are satisfied (e.g., the subject is exhibiting severe symptoms of a nitrogen retention disorder).

[0039] In certain embodiments, the target range for plasma PAA:PAGN ratio may comprise one or more subranges, with subjects falling within different subranges being treated differently despite falling within the target range. For example, where a target range is 1 to 2.5, a subject exhibiting a PAA:PAGN ratio below 1 or above 2.5 may be classified as requiring an adjustment in PAA prodrug dosage. Within the target range, subjects with a PAA:PAGN ratio falling within a particular subrange may be treated as properly dosed, improperly dosed (i.e., requiring a dosage adjustment), or properly dosed but requiring more frequent monitoring. For example, subjects having a PAA:PAGN ratio greater than 2 but not greater than 2.5 may be classified as properly dosed but requiring more frequent monitoring.

[0040] In certain embodiments, subrange boundaries or the treatment of subjects falling within a particular subrange will depend in part on a subject's specific characteristics, including for example biochemical profile or clinical characteristics such as target nitrogen excretion, actual nitrogen excretion, symptom severity, disorder duration, age, or overall health. For example, in certain embodiments a first subject with a PAA:PAGN ratio falling within the subrange of 2 to 2.5 may be classified as properly dosed but requiring frequent monitoring, while a second subject falling within the same subrange may be classified as requiring a decreased dosage of PAA prodrug. Similarly, a first subject with a PAA:PAGN ratio falling within the subrange of 1 to 1.5 may be classified as properly dosed but requiring frequent monitoring, while a second subject falling within the same subrange may be classified as requiring an increased dosage of PAA prodrug. For example, a subject who has recently exhibited particularly acute symptoms associated with a particular disorder may be classified as requiring an increased dosage of PAA prodrug when exhibiting a PAA:PAGN ratio of 1 to 1.5, while a subject who is clinically controlled may be classified as properly dosed despite a ratio falling within the same subrange.

[0041] In certain embodiments, methods are provided herein for treating a nitrogen retention disorder or a condition for which PAA prodrug administration is expected to be beneficial in a subject that has previously received a first dosage of a PAA prodrug. These methods comprise measuring plasma PAA and PAGN levels, calculating the plasma PAA:PAGN ratio, determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, and administering a second dosage of the PAA prodrug. In certain embodiments, the target range for PAA:PAGN ratio is 1 to 2.5 or 1 to 2. In certain of these embodiments, the second dosage is greater than the first dosage if the PAA:PAGN ratio is less than 1 (i.e., the dosage is increased) and less than the first dosage if the PAA:PAGN ratio is greater than 2.5 (i.e., the dosage is decreased). In other embodiments, the second dosage may or may not be greater than the first dosage if the PAA:PAGN ratio is less than 1, depending on one or more other characteristics of the subject. In certain embodiments, the second dosage is equal to the first dosage when the PAA:PAGN ratio is 1 to 2.5, i.e., falling within the target range. In certain embodiments, the target range is divided into one or more subranges. In certain of these embodiments, the second dosage may be equal to the first dosage if the PAA:PAGN ratio is 1 to 1.5 or 2 to 2.5, but the

subject may be subjected to more frequent monitoring. In certain other embodiments, the second dosage may be greater than the first dosage if the PAA:PAGN ratio is 1 to 1.5 or 1 to 2 and the subject has recently exhibited particularly acute symptoms of a nitrogen retention disorder or another condition for which PAA prodrug administration is expected to be beneficial. Similarly, the second dosage may be less than the first dosage if the PAA:PAGN ratio is greater than 1.5 or 2 but not greater than 2.5, depending on the subject's specific characteristics. In certain embodiments, the increase or decrease in the second dosage versus the first dosage depends on the precise plasma PAA:PAGN ratio. For example, where the plasma PAA:PAGN ratio is only slightly less than 1, the dosage may be increased only slightly, but where the PAA:PAGN ratio is significantly less than 1, the dosage may be increased more. Similarly, the decrease in dosage for subjects exhibiting a ratio above 2.5 may vary depending on how far above 2.5 the ratio extends. In certain embodiments, measurement of plasma PAA and PAGN ratio takes place after the PAA prodrug has had sufficient time to reach steady state (e.g., 48 hours, 48 to 72 hours, 72 hours to 1 week, 1 week to 2 weeks, or greater than 2 weeks after PAA prodrug administration). In certain embodiments, the above steps may be repeated until a desired plasma PAA:PAGN ratio (e.g., 1 to 2.5 or 1 to 2) is achieved. For example, the methods may comprise measuring plasma PAA and PAGN levels after administration of the second dosage, calculating the plasma PAA:PAGN ratio, determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within the target range, and administering a third dosage of the PAA prodrug.

[0042] In certain embodiments, methods are provided for treating a nitrogen retention disorder or a condition for which PAA prodrug administration is expected to be beneficial in a subject that has not previously been administered a PAA prodrug. These methods comprise administering a first dosage of a PAA prodrug, measuring plasma PAA and PAGN levels, calculating the plasma PAA:PAGN ratio, determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, and administering a second dosage of the PAA prodrug. In certain embodiments, the target range for PAA:PAGN ratio is 1 to 2.5 or 1 to 2. In certain of these embodiments, the second dosage is greater than the first dosage if the PAA:PAGN ratio is less than 1 (i.e., the dosage is increased) and less than the first dosage if the PAA:PAGN ratio is greater than 2.5 (i.e., the dosage is decreased). In other embodiments, the

second dosage may or may not be greater than the first dosage if the PAA:PAGN ratio is less than 1, depending on one or more additional characteristics of the subject. In certain embodiments, the second dosage is equal to the first dosage when the PAA:PAGN ratio is 1 to 2.5, i.e., falling within the target range. In certain embodiments, the target range is divided into one or more subranges. In certain of these embodiments, the second dosage may be equal to the first dosage if the PAA:PAGN ratio is 1 to 1.5 or 2 to 2.5, but the subject may be subjected to more frequent monitoring. In certain other embodiments, the second dosage may be greater than the first dosage if the PAA:PAGN ratio is 1 to 1.5 or 1 to 2 and the subject has recently exhibited particularly acute symptoms of a nitrogen retention disorder or another condition for which PAA prodrug administration is expected to be beneficial. Similarly, the second dosage may be less than the first dosage if the PAA:PAGN ratio is greater than 1.5 or 2 but not greater than 2.5, depending on the subject's specific clinical or biochemical characteristics. In certain embodiments, the increase or decrease in the second dosage versus the first dosage depends on the precise plasma PAA:PAGN ratio. For example, where the plasma PAA:PAGN ratio is only slightly less than 1, the dosage may be increased only slightly, but where the PAA:PAGN ratio is significantly less than 1, the dosage may be increased more. Similarly, the decrease in dosage for subjects exhibiting a ratio above 2.5 may vary depending on how far above 2.5 the ratio extends. In certain embodiments, measurement of plasma PAA and PAGN ratio takes place after the PAA prodrug has had sufficient time to reach steady state (e.g., 48 hours, 48 to 72 hours, 72 hours to 1 week, 1 week to 2 weeks, or greater than 2 weeks after PAA prodrug administration). In certain embodiments, the above steps may be repeated until a desired plasma PAA:PAGN ratio (e.g., 1 to 2.5 or 1 to 2) is achieved. For example, the methods may comprise measuring plasma PAA and PAGN levels after administration of the second dosage, calculating the plasma PAA:PAGN ratio, determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within the target range, and administering a third dosage of the PAA prodrug.

[0043] A method of administering a PAA prodrug to a subject with a nitrogen retention disorder or another condition for which PAA prodrug administration is expected to be beneficial. These methods comprise administering a first dosage of the PAA prodrug, measuring plasma PAA and PAGN levels, calculating the plasma PAA:PAGN ratio, determining whether the PAA prodrug

dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, and administering a second dosage of the PAA prodrug. In certain embodiments, the target range for PAA:PAGN ratio is 1 to 2.5 or 1 to 2. In certain of these embodiments, the second dosage is greater than the first dosage if the PAA:PAGN ratio is less than 1 (i.e., the dosage is increased) and less than the first dosage if the PAA:PAGN ratio is greater than 2.5 (i.e., the dosage is decreased). In other embodiments, the second dosage may or may not be greater than the first dosage if the PAA:PAGN ratio is less than 1, depending on one or more additional characteristics of the subject. In certain embodiments, the second dosage is equal to the first dosage when the PAA:PAGN ratio is 1 to 2.5, i.e., falling within the target range. In certain embodiments, the target range is divided into one or more subranges. In certain of these embodiments, the second dosage may be equal to the first dosage if the PAA:PAGN ratio is 1 to 1.5 or 2 to 2.5, but the subject may be subjected to more frequent monitoring. In certain other embodiments, the second dosage may be greater than the first dosage if the PAA:PAGN ratio is 1 to 1.5 or 1 to 2 and the subject has recently exhibited particularly acute symptoms of a nitrogen retention disorder or another condition for which PAA prodrug administration is expected to be beneficial. Similarly, the second dosage may be less than the first dosage if the PAA:PAGN ratio is greater than 1.5 or 2 but not greater than 2.5, depending on the subject's specific biochemical or clinical characteristics. In certain embodiments, the increase or decrease in the second dosage versus the first dosage depends on the precise plasma PAA:PAGN ratio. For example, where the plasma PAA:PAGN ratio is only slightly less than 1, the dosage may be increased only slightly, but where the PAA:PAGN ratio is significantly less than 1, the dosage may be increased more. Similarly, the decrease in dosage for subjects exhibiting a ratio above 2.5 may vary depending on how far above 2.5 the ratio extends. In certain embodiments, measurement of plasma PAA and PAGN ratio takes place after the PAA prodrug has had sufficient time to reach steady state (e.g., 48 hours, 48 to 72 hours, 72 hours to 1 week, 1 week to 2 weeks, or greater than 2 weeks after PAA prodrug administration). In certain embodiments, the above steps may be repeated until a desired plasma PAA:PAGN ratio (e.g., 1 to 2.5 or 1 to 2) is achieved. For example, the methods may comprise measuring plasma PAA and PAGN levels after administration of the second dosage, calculating the plasma PAA:PAGN ratio, determining whether the PAA

prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within the target range, and administering a third dosage of the PAA prodrug.

[0044] In certain embodiments, methods are provided herein for achieving a target plasma PAA:PAGN ratio in a subject with a nitrogen retention disorder or another condition for which PAA prodrug administration is expected to be beneficial. These methods comprise administering a first dosage of a PAA prodrug, measuring plasma PAA and PAGN levels, calculating the plasma PAA:PAGN ratio, determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, and administering a second dosage of the PAA prodrug based on the PAA:PAGN ratio. If the PAA:PAGN ratio is above the target range, the second dosage is less than the first dosage. If the PAA:PAGN ratio is below the target range, the second dosage is greater than the first dosage. These steps are repeated until a target plasma PAA:PAGN ratio is achieved. In certain embodiments, the target ratio falls within a target range of 1 to 2.5 or 1 to 2. In certain embodiments, the increase or decrease in the second dosage versus the first dosage depends on the precise plasma PAA:PAGN ratio. For example, where the plasma PAA:PAGN ratio is only slightly less than 1, the dosage may be increased only slightly, but where the PAA:PAGN ratio is significantly less than 1, the dosage may be increased more. Similarly, the decrease in dosage for subjects exhibiting a ratio above 2.5 may vary depending on how far above 2.5 the ratio extends. In certain embodiments, measurement of plasma PAA and PAGN ratio takes place after the PAA prodrug has had sufficient time to reach steady state (e.g., 48 hours, 48 to 72 hours, 72 hours to 1 week, 1 week to 2 weeks, or greater than 2 weeks after PAA prodrug administration).

[0045] In certain embodiments, methods are provided for evaluating the dosage of a PAA prodrug in a subject who has previously been administered a first dosage of a PAA prodrug. These methods comprise measuring plasma PAA and PAGN levels, calculating the plasma PAA:PAGN ratio, and determining whether the first dosage of the PAA prodrug is effective based on whether the PAA:PAGN ratio falls within a target range. In certain embodiments, the target range for PAA:PAGN ratio is 1 to 2.5 or 1 to 2. In certain of these embodiments, the first dosage is considered too low if the PAA:PAGN ratio is less than 1, and too high if the PAA:PAGN ratio is greater than 2.5. In other embodiments, the first dosage is considered potentially too low if

PAA:PAGN ratio is less than 1, with a final decision depending on one or more additional characteristics of the subject. In certain embodiments, the target range is divided into one or more subranges. In certain of these embodiments, the first dosage is considered potentially effective if the PAA:PAGN ratio is 1 to 1.5 or 2 to 2.5, but the subject may be subjected to more frequent monitoring. In certain other embodiments, the first dosage may be considered too low if the PAA:PAGN ratio is 1 to 1.5 or 1 to 2 and the subject has recently exhibited particularly acute symptoms of a nitrogen retention disorder or another condition for which PAA prodrug administration is expected to be beneficial. Similarly, in certain embodiments the first dosage may be considered too high if the PAA:PAGN ratio is greater than 1.5 or 2 but not greater than 2.5, depending on the subject's specific biochemical or clinical characteristics. In certain embodiments, measurement of plasma PAA and PAGN ratio takes place after the PAA prodrug has had sufficient time to reach steady state (e.g., 48 hours, 48 to 72 hours, 72 hours to 1 week, 1 week to 2 weeks, or greater than 2 weeks after PAA prodrug administration). In certain embodiments, the methods further comprise a step of administering a second dosage that differs from the first dosage, and in certain of these embodiments the above steps may be repeated until a desired plasma PAA:PAGN ratio (e.g., 1 to 2.5 or 1 to 2) is achieved. For example, the methods may comprise administering a second dosage that differs from the first dosage, measuring plasma PAA and PAGN levels after administration of the second dosage, calculating the plasma PAA:PAGN ratio, and determining whether the second dosage of the PAA prodrug is effective based on whether the PAA:PAGN ratio falls within a target range.

[0046] In certain embodiments, methods are provided for adjusting the dosage of a PAA prodrug in a subject who has previously been administered a first dosage of a PAA prodrug. These methods comprise measuring plasma PAA and PAGN levels, calculating the plasma PAA:PAGN ratio, and determining whether to adjust the dosage of the PAA prodrug based on whether the PAA:PAGN ratio falls within a target range. In certain embodiments, the target range for PAA:PAGN ratio is 1 to 2.5 or 1 to 2. In certain of these embodiments where the target range is 1 to 2.5, a PAA:PAGN ratio of less than 1 indicates the PAA prodrug dosage needs to be adjusted upwards, while a PAA:PAGN ratio above 2.5 indicates the PAA prodrug dosage needs to be adjusted downwards. In other embodiments, a PAA:PAGN ratio of less than 1 indicates that the

PAA prodrug dosage potentially needs to be adjusted upwards, with a final decision depending on one or more additional characteristics of the subject. In certain embodiments, the target range is divided into one or more subranges. In certain of these embodiments, a PAA:PAGN ratio of 1 to 1.5 or 2 to 2.5 indicates that the dosage need not be adjusted, but that the subject should be subjected to more frequent monitoring. In certain other embodiments, a PAA:PAGN ratio of 1 to 1.5 or 1 to 2 indicates that the dosage needs to be increased when the subject has recently exhibited particularly acute symptoms of a nitrogen retention disorder or another condition for which PAA prodrug administration is expected to be beneficial. Similarly, in certain embodiments a PAA:PAGN ratio greater than 1.5 or 2 but not greater than 2.5 may indicate that the dosage needs to be decreased, depending on the subject's specific biochemical or clinical characteristics. In certain embodiments, measurement of plasma PAA and PAGN ratio takes place after the PAA prodrug has had sufficient time to reach steady state (e.g., 48 hours, 48 to 72 hours, 72 hours to 1 week, 1 week to 2 weeks, or greater than 2 weeks after PAA prodrug administration). In certain embodiments where a determination is made that the dosage needs to be adjusted, the methods further comprise a step of administering a second dosage that differs from the first dosage, and in certain of these embodiments the above steps may be repeated until a desired plasma PAA:PAGN ratio (e.g., 1 to 2.5 or 1 to 2) is achieved. For example, the methods may comprise administering a second dosage that differs from the first dosage, measuring plasma PAA and PAGN levels after administration of the second dosage, calculating the plasma PAA:PAGN ratio, and determining whether the second dosage of the PAA prodrug needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range. In certain embodiments, the increase or decrease in the second dosage versus the first dosage depends on the precise plasma PAA:PAGN ratio. For example, where the plasma PAA:PAGN ratio is only slightly less than 1, the dosage may be increased only slightly, but where the PAA:PAGN ratio is significantly less than 1, the dosage may be increased more. Similarly, the decrease in dosage for subjects exhibiting a ratio above 2.5 may vary depending on how far above 2.5 the ratio extends.

[0047] In certain embodiments, methods are provided for optimizing the therapeutic efficacy of a PAA prodrug for use in treating a nitrogen retention disorder in a subject. These methods comprise measuring plasma PAA and PAGN levels in a subject who has previously been

administered a PAA prodrug, calculating the plasma PAA:PAGN ratio, determining whether to adjust the dosage of the PAA prodrug based on whether the PAA:PAGN ratio falls within a target range, and administering an adjusted dosage of the PAA prodrug as necessary. These steps are repeated until the subject exhibits a plasma PAA:PAGN ratio falling within the target range (e.g., 1 to 2.5 or 1 to 2). In certain embodiments where the target range is 1 to 2.5, a plasma PAA:PAGN ratio of less than 1 indicates that the dosage needs to be adjusted upwards, while a ratio greater than 2.5 indicates that the dosage needs to be decreased. In certain embodiments, the target range is divided into one or more subranges. In certain of these embodiments, a PAA:PAGN ratio of 1 to 1.5 or 2 to 2.5 indicates that the dosage does not need to be adjusted, but that the subject should be subjected to more frequent monitoring. In certain other embodiments, a PAA:PAGN ratio of 1 to 1.5 or 1 to 2 indicates that the dosage needs to be increased when the subject has recently exhibited particularly acute symptoms of a nitrogen retention disorder or another condition for which PAA prodrug administration is expected to be beneficial. Similarly, in certain embodiments a PAA:PAGN ratio greater than 1.5 or 2 but not greater than 2.5 may indicate that the dosage needs to be decreased, depending on the subject's specific biochemical or clinical characteristics. In certain embodiments, measurement of plasma PAA and PAGN ratio takes place after the PAA prodrug has had sufficient time to reach steady state (e.g., 48 hours, 48 to 72 hours, 72 hours to 1 week, 1 week to 2 weeks, or greater than 2 weeks after PAA prodrug administration). In certain embodiments, the magnitude of the increase or decrease in dosage may be based on the precise PAA:PAGN ratio. For example, a PAA:PAGN ratio that is slightly less than 1 may indicate that the dosage needs to be increased slightly, while a ratio significantly less than 1 may indicate the dosage needs to be increased to a greater degree. In certain embodiments, the above steps are repeated until the subject exhibits a PAA:PAGN ratio falling within the target range.

[0048] In certain embodiments, methods are provided for determining whether a prescribed first dosage of a PAA prodrug can be safely administered to a subject. These methods comprise administering the prescribed first dosage to the subject, measuring plasma PAA and PAGN levels, calculating the plasma PAA:PAGN ratio, and determining whether the prescribed first dosage is safe for the subject based on whether the PAA:PAGN ratio falls above a target range, wherein a PAA:PAGN ratio falling above the target range indicates that the first dosage cannot be or

potentially cannot be safely administered to the subject. In certain embodiments, the target range for PAA:PAGN ratio is 1 to 2.5 or 1 to 2. In certain of these embodiments where the target range is 1 to 2.5, a PAA:PAGN ratio above 2.5 indicates the PAA prodrug dosage is unsafe and needs to be adjusted downwards. In certain embodiments, the target range is divided into one or more subranges. In certain of these embodiments, a PAA:PAGN ratio of 2 to 2.5 indicates that the first dosage is safe, but that the subject should be subjected to more frequent monitoring. In other embodiments, a PAA:PAGN ratio of 2 to 2.5 indicates that the first dosage is potentially unsafe, with a final determination of safety taking into account the subject's specific biochemical or clinical characteristics. In certain embodiments, measurement of plasma PAA and PAGN ratio takes place after the PAA prodrug has had sufficient time to reach steady state (e.g., 48 hours, 48 to 72 hours, 72 hours to 1 week, 1 week to 2 weeks, or greater than 2 weeks after PAA prodrug administration). In certain embodiments where a determination is made that the first dosage is unsafe and needs to be decreased, the methods further comprise a step of administering a second dosage that is lower than the first dosage, and in certain of these embodiments the above steps may be repeated until a desired plasma PAA:PAGN ratio (e.g., 1 to 2.5 or 1 to 2) is achieved. For example, the methods may comprise administering a second dosage that is lower than the first dosage, measuring plasma PAA and PAGN levels after administration of the second dosage, calculating the plasma PAA:PAGN ratio, and determining whether the second dosage of the PAA prodrug can be safely administered to the subject based on whether the PAA:PAGN ratio falls above a target range.

[0049] In certain embodiments, methods are provided for determining whether a prescribed first dosage of a PAA prodrug will be effective for treating a nitrogen retention disorder or another disorder for which PAA prodrug administration is expected to be beneficial. These methods comprise administering the prescribed first dosage to the subject, measuring plasma PAA and PAGN levels, calculating the plasma PAA:PAGN ratio, and determining whether the prescribed first dosage will be effective for the subject based on whether the PAA:PAGN ratio falls below a target range, wherein a PAA:PAGN ratio falling below the target range indicates that the first dosage will not be or potentially will not be effective for treating a disorder. In certain embodiments, the target range for PAA:PAGN ratio is 1 to 2.5 or 1 to 2. In certain of these embodiments where the target range is 1 to 2.5, a PAA:PAGN ratio below 1 indicates the PAA

prodrug dosage is unlikely to be effective and needs to be adjusted upwards. In other embodiments, a PAA:PAGN ratio below 1 indicates that the first dosage is potentially ineffective, with a final determination of whether the dosage is likely to be ineffective based on the subject's specific biochemical or clinical characteristics. In certain embodiments, the target range is divided into one or more subranges. In certain of these embodiments, a PAA:PAGN ratio of 1 to 1.5 indicates that the first dosage is likely to be effective, but that the subject should be subjected to more frequent monitoring. In other embodiments, a PAA:PAGN ratio of 1 to 1.5 indicates that the first dosage is potentially ineffective, with a final determination of whether the dosage is likely to be ineffective taking into account the subject's specific biochemical or clinical characteristics. In certain embodiments, measurement of plasma PAA and PAGN ratio takes place after the PAA prodrug has had sufficient time to reach steady state (e.g., 48 hours, 48 to 72 hours, 72 hours to 1 week, 1 week to 2 weeks, or greater than 2 weeks after PAA prodrug administration). In certain embodiments where a determination is made that the first dosage is likely to be ineffective and needs to be increased, the methods further comprise a step of administering a second dosage that is higher than the first dosage, and in certain of these embodiments the above steps may be repeated until a desired plasma PAA:PAGN ratio (e.g., 1 to 2.5 or 1 to 2) is achieved. For example, the methods may comprise administering a second dosage that is higher than the first dosage, measuring plasma PAA and PAGN levels after administration of the second dosage, calculating the plasma PAA:PAGN ratio, and determining whether the second dosage of the PAA prodrug is likely to be ineffective for treating a disorder based on whether the PAA:PAGN ratio falls above a target range.

[0050] Provided herein in certain embodiments are methods for monitoring therapy with a PAA prodrug in patients with a nitrogen retention disorder. These methods comprise administering a PAA prodrug to the subject, measuring plasma PAA and PAGN levels, and calculating the plasma PAA:PAGN ratio. In these methods, a PAA:PAGN ratio falling within a target range (e.g., 1 to 2.5 or 1 to 2) indicates that the therapy is effective, while a ratio falling outside this range indicates that the therapy may need to be adjusted. In certain embodiments, the plasma PAA:PAGN ratio is compared to a previously obtained PAA:PAGN ratio from the same subject to evaluate the effectiveness of PAA prodrug administration.

[0051] In certain embodiments, the methods provided herein may be used in conjunction with the methods described in WO09/134460 and WO10/025303. In these embodiments, urinary PAGN levels may be determined in addition to plasma PAA:PAGN ratio, with both measurements being used to evaluate or adjust PAA prodrug dosage.

[0052] A "PAA prodrug" as used herein refers to any drug that contains or is converted to PAA following administration to a subject, or to any pharmaceutically acceptable salt, ester, acid, or derivative thereof. A PAA prodrug may be administered via any route, including oral or parenteral administration. A PAA prodrug may be converted directly to PAA (e.g., a salt or ester of PAA; PBA or a salt or ester thereof such as NaPBA), or it may be converted to PAA via an intermediate (e.g., a pre-prodrug such as HPN-100). Other examples of PAA prodrugs include butyroyloxymethyl-4-phenylbutyrate.

[0053] An adjustment to the dosage of a PAA prodrug as discussed herein may refer to a change in the amount of drug per administration (e.g., an increase from a first dosage of 3 mL to a second dosage of 6 mL), a change in the number of administration within a particular time period (e.g., an increase from once a day to twice a day), or any combination thereof.

[0054] A "subject in need thereof" as used herein refers to any individual having a condition or suspected of having a condition for which administration of a PAA prodrug is expected to be beneficial. For example, a subject may be an individual with a nitrogen retention disorder or suspected of having a nitrogen retention disorder, including for example UCD, HE, and/or kidney failure/ESRD (Lee 2010; McGuire 2010; Lichter 2011). Likewise, a subject may have or be suspected of having another condition for which PAA prodrug administration is expected to be beneficial, including for example cancer (Thiebault 1994; Thiebault 1995), neurodegenerative disorders such as Huntington's Disease (Hogarth 2007), amyotrophic lateral sclerosis (ALS) (Cudkowicz 2009), and spinal muscular atrophy (SMA) (Mercuri 2004; Brahe 2005), metabolic disorders (e.g., maple syrup urine disease (MSUD) (Bruneti-Pieri 2011), or sickle cell disease (Hines 2008).

[0055] A subject that has previously been administered a PAA prodrug may have been administered the drug for any duration of time sufficient to reach steady state. For example, the

subject may have been administered the drug over a period of 2 to 7 days, 1 week to 2 weeks, 2 weeks to 4 weeks, 4 weeks to 8 weeks, 8 weeks to 16 weeks, or longer than 16 weeks.

[0056] A "PAA prodrug" as used herein refers to any drug that contains or is converted to PAA following administration to a subject, or to any pharmaceutically acceptable salt, ester, acid, or derivative thereof. A PAA prodrug may be administered via any route, including oral or parenteral administration. A PAA prodrug may be converted directly to PAA (e.g., PBA or a salt thereof such as NaPBA), or it may be converted to PAA via an intermediate (e.g., a pre-prodrug such as HPN-100). Other examples of PAA prodrugs include butyroyloxymethyl-4-phenylbutyrate.

[0057] An adjustment to the dosage of a PAA prodrug as discussed herein may refer to a change in the amount of drug per administration (e.g., an increase from a first dosage of 3 mL to a second dosage of 6 mL), a change in the number of administration within a particular time period (e.g., an increase from once a day to twice a day), or any combination thereof.

[0058] The terms "treat," "treating," or "treatment" as used herein may refer to preventing a disorder, slowing the onset or rate of development of a disorder, reducing the risk of developing a disorder, preventing or delaying the development of symptoms associated with a disorder, reducing or ending symptoms associated with a disorder, generating a complete or partial regression of a disorder, or some combination thereof. For example, where the disorder being treated is a nitrogen retention disorder, "treating" may refer to lowering waste nitrogen levels below a threshold level, preventing waste nitrogen levels from reaching a threshold level, decreasing the likelihood of waste nitrogen levels exceeding a threshold level, reducing or ending symptoms associated with elevated waste nitrogen levels, or a combination thereof.

[0059] With regard to the methods of treatment disclosed herein, interpretation of the PAA:PAGN ratio must be performed in the context of the therapeutic objective. For example, in subjects being treated for a nitrogen retention disorder, the therapeutic objective is elimination of waste nitrogen in the form of PAGN. In subjects being treated for other disorders for which PAA prodrug administration is expected to be beneficial (e.g., neurodegenerative disorders, MSUD), the therapeutic objective is safely achieving target plasma levels of PAA and/or PBA.

[0060] Any methods known in the art may be used to obtain a plasma blood sample. For example, blood from a subject may be drawn into a tube containing heparin or

ethylenediaminetetraacetic acid (EDTA). In certain embodiments, the sample can be placed on ice and centrifuged to obtain plasma within 15 minutes of collection, stored at 2-8°C (36-46°F) and analyzed within 3 hours of collection. In other embodiments, the blood plasma sample is snap frozen, stored at ≤-18°C (≤0°F) and analyzed at a later time. For example, the sample may be analyzed at 0-12 hours, 12-24 hours, 24-48, 48-96 hours after freezing, or within any other timeframe over which the sample has demonstrated stability. In certain of these embodiments, the blood sample is stored at a temperature between 0-15°C, such as 2-8°C. In other embodiments, the blood sample is stored below 0°C or below -18°C.

[0061] Measurement of PAA and PAGN levels in a plasma sample is carried out using techniques known in the art. For example, PAA and PAGN levels may be measured using liquid chromatography/mass spec analyses.

[0062] Any combination of embodiments described herein can be envisioned. Although individual features may be included in different claims, these may be advantageously combined.

[0063] The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention. It will be understood that many variations can be made in the procedures herein described while still remaining within the bounds of the present invention. It is the intention of the inventors that such variations are included within the scope of the invention.

EXAMPLES

Example 1: Analysis of PAA:PAGN ratio in UCD and HE subjects:

[0064] Plasma PAA and PAGN levels and PAA:PAGN ratio were analyzed in more than 4000 plasma samples obtained from various clinical trials of healthy adults, severely hepatic impaired adults with clinically decompensated Child-Pugh B or C cirrhosis, and UCD patients ages 29 days or older. Healthy and hepatically impaired adults received HPN-100, while UCD subjects received both HPN-100 and NaPBA. Clinical trial populations are summarized in Tables 1 and 2.

Table 1: Clinical studies and analysis populations

Study Group	Description	Demographics	Protocols Included	Analysis Populations
1	Short-term (<= 2-4 weeks) exposure in UCD subjects	Adults and children ages 29 days or greater (N=81)	UP 1204-003 HPN-100-005SO HPN-100-006 HPN-100-012	A, B
2	Long-term exposure in UCD and HE subjects	Adults and children ages 6 years or greater (N=180)	HPN-100-005SE HPN-100-007 HPN-100-008 Part B	A
3	Short-term (<= 4 weeks) exposure in hepatic impaired subjects	Adults (N=15)	HPN-100-008 Part A	A, B
4	Short-term exposure (<= 4 weeks) in healthy subjects	Adults (N=98)	HPN-100-010	A, B

Table 2: Demographics and number of samples used

	Attribute	No. of subjects		No. of sample points (Population A)		No. of time-specific PK sample points (Population B)	
		Count	Percent	Count	Percent	Count	Percent
Population	Healthy	86	17.0	2126	34.4	2126	38.5
	Hepatic Encephalopathy (HE)	103	20.4	830	13.4	830	15.0
	UCD	158	31.3	1616	26.1	1281	23.2
	Total	**347**	**100.0**	**4572**	**100.0**	**4237**	**100.0**
Age	29 days -< 6 yrs	15	4.3	110	2.4	110	2.6
	6 -< 18 yrs	47	13.5	373	8.2	213	5.0
	18+ yrs	285	82.1	4089	89.4	3914	92.4
Sex	F	199	57.3	2394	52.4	2152	50.8
	M	148	42.7	2178	47.6	2085	49.2

[0065] Analysis Population A consisted of quantifiable levels of PAA and PAGN metabolites derived from all studies described above. All PAA and PAGN levels used for analysis came from blood samples drawn once dosing with NaPBA or HPN-100 had reached steady state. Analysis Population B consisted of quantifiable levels of PAA and PAGN metabolites during studies in which pharmacokinetics were analyzed and for which blood draws were performed over 12 or 24 hours at steady state and for which the timing of the blood sample in relation to dosing was known. Subjects in study groups 1, 3 and 4 above contributed to these points. Analysis Population B was

the source of analyses that examined how PAA levels changed with time relative to dosing, where dosing could have been with either NaPBA or HPN-100. To be eligible for Analysis Population B, the time of the blood draw relative to the time of initiation of dosing during the dosing period had to have been recorded.

[0066] Data on metabolite levels were pooled across a wide range of age levels- infants, toddlers, children, adolescents, and adults. All children, defined as ages under 18, were UCD patients. The majority of the blood sampling points came from adults (89.4%). Newborn infants (< 29 days old) were not studied in any of the clinical trials for the investigational agent HPN-100. The population of blood sampling points were roughly equally divided between female and male (57.3% female, 42.7% male).

[0067] To examine the predictive ability of PAA:PAGN ratios, a subject was considered to have achieved a high value of PAA if any PAA value up to 24 hours since initiation of dosing equaled or exceeded 400 μg/mL or equaled or exceeded 500 μg/mL. PAA:PAGN ratios were grouped into one of three categorization schemes: a.) [0-<= 2.0] , [> 2.0] , b.) [0- <= 2.5, > 2.5], c.) [0- <= 3.0, > 3.0]. The repeated measures categorical outcome was modeled using GEE with a logit link function, ratio category as the independent variable, and SUBJECTID as the repeated measures factor. Confidence intervals for the predicted probabilities were computed by bootstrap estimation of 1000 resamplings of the original data, as detailed in Davison & Hinkley, "Bootstrap Methods and Their Application," Cambridge Univ. Press (1997), pp. 358-362.

[0068] Results are summarized in Figures 2-5. A striking curvilinear relationship was observed between plasma PAA levels and PAA:PAGN ratio at any given timepoint. Figure 2A shows the relationship between the ratio of PAA:PAGN concentrations and absolute PAA levels in micrograms per milliliter among blood samples that had quantifiable values for both PAA and PAGN. The ratio axis (i.e. 'X' axis) is plotted on a logarithmic (base e) scale. For ratios less than 1.0, increases in ratio are not associated with correspondingly elevated or increased levels of PAA. Above ratios of 1.0, there is a gradual increase in PAA levels, and a noticeable upswing in PAA levels that begins in the vicinity of a ratio of 2.0. This finding suggests that when the ratio of PAA precursor to PAGN product approaches higher values, the values of PAA are also correspondingly

high. This increase in the ratio of precursor (PAA) to product (PAGN) implies ineffective PAA to PAGN conversion, regardless of whether the PAA is derived from HPN-100 or NaPBA.

[0069] To determine whether excessive PAA build-up is a function of dosing, the plots mentioned above were repeated, but this time adjusting for assigned dose level of NaPBA or HPN-100 at the time of the blood draw. Since the UCD population consisted of a mixture of children and adults undergoing both short-term therapy and long-term therapy, total assigned daily dose for UCD patients was standardized to body surface area and reported in PBA-equivalent grams meter^2. Healthy and HE subjects were all adults and their assigned dose was not adjusted by body surface area. Dose levels for healthy and HE subjects were reported in HPN-100 equivalent mL. Dose levels for UCD subjects were reported in NaPBA-equivalent grams.

[0070] The excess of PAA over PAGN, indicated by larger ratios as PAA increases, was evident across all dosage groups, disease populations, and types of treatment in UCD patients (i.e., applies to both NaPBA and HPN-100). This finding suggests that analysis of the precursor (PAA) to product (PAGN) ratio may be predictive of the efficiency of conversion among patients with or without liver dysfunction (UCD patients have normal liver function apart from their urea cycle dysfunction) and independently of dose. As a corollary, the presence of liver dysfunction (e.g. cirrhosis) by itself, is not necessarily a reliable determinant of whether a particular patient is at risk for high PAA levels.

[0071] The ability of PAA:PAGN ratios to predict extremely high plasma PAA concentrations was determined by modeling the probability that a subject would exceed a PAA value of 400 or 500 μg/mL anytime during a 24 hour dosing period, based on the ratio of PAA to PAGN computed at pre-dose (presumably trough), 12 hours after dosing (presumably peak), and the maximum ratio encountered anytime between pre-dose and 12 hours post-dose. This interval of 0-12 hours was chosen for practical reasons, as it would encompass the entire interval corresponding to the usual outpatient visit.

[0072] Since subjects could have multiple dosing periods within a given clinical study, the probability was modeled using Generalized Estimating Equations. Three categorizations of ratios were modeled: a.) [0-<= 2.0] [> 2.0] , b.) [0- <= 2.5, > 2.5], c.) [0- <= 3.0, > 3.0]. The models were

repeated with PAA values greater than or equal to 500 μg/mL considered extreme. Results are summarized in Table 3.

Table 3: Probabilities of extreme PAA values encountered during 24 hour PK sampling with PAA:PAGN ratios (all subjects combined)

PAA Value Considered High		Time of Blood Draw Used For Ratio Classification	Observed Ratio of PAA/PAGN	Probability that a Subject With This Ratio Will Exceed High Value* (%)	Bootstrapped 95% Confidence Interval**
[<=2.0, >2.0]	>=400 μg/mL	t=0 (fasting)	<= 2.0	0.005 (0.5%)	0.004, 0.020
			> 2.0	0.164 (16.4%)	0.041, 0.281
		t = 12 hours	<= 2.0	0.003 (0.3%)	0.004, 0.021
			> 2.0	0.227 (22.7%)	0.048, 0.412
		MAX(0-12)	<= 2.0	0.002 (0.2%)	0.004, 0.010
			> 2.0	0.143 (14.3%)	0.036, 0.263
	>=500 μg/mL	t=0 (fasting)	<= 2.0	did not converge	
			> 2.0		
		t = 12 hours	<= 2.0	did not converge	
			> 2.0		
		MAX(0-12)	<= 2.0	did not converge	
			> 2.0		
[<=2.5, >2.5]	>=400 μg/mL	t=0 (fasting)	<= 2.5	0.008 (0.8%)	0.004, 0.023
			> 2.5	0.191 (19.1%)	0.053, 0.366
		t = 12 hours	<= 2.5	0.007 (0.7%)	0.004, 0.016
			> 2.5	0.364 (36.4%)	0.125, 0.752
		MAX(0-12)	<= 2.5	0.003 (0.3%)	0.004, 0.013
			> 2.5	0.200 (20.0%)	0.050, 0.381
	>=500 μg/mL	t=0 (fasting)	<= 2.5	0.003 (0.3%)	0.004, 0.011
			> 2.5	0.084 (8.4%)	0.029, 0.214
		t = 12 hours	<= 2.5	did not converge	
			> 2.5		
		MAX(0-12)	<= 2.5	did not converge	
			> 2.5		
[<=3, >3]	>=400 μg/mL	t=0 (fasting)	<= 3.0	0.010 (1.0%)	0.004, 0.025
			> 3.0	0.205 (20.5%)	0.059, 0.398
		t = 12 hours	<= 3.0	0.013 (1.3%)	0.004, 0.028
			> 3.0	0.250 (25.0%)	0.113, 0.576
		MAX(0-12)	<= 3.0	0.003 (0.3%)	0.004, 0.014
			> 3.0	0.229 (22.9%)	0.059, 0.438
	>=500 μg/mL	t=0 (fasting)	<= 3.0	0.003 (0.3%)	0.004, 0.010
			> 3.0	0.102 (10.2%)	0.032, 0.255
		t = 12 hours	<= 3.0	did not converge	
			> 3.0		
		MAX(0-12)	<= 3.0	did not converge	
			> 3.0		

Analysis repeated for each ratio cut off category independently.

* Probability derived from Generalized Estimating Equations model with logit link function.

** Confidence interval derived from method disclosed in Davison & Hinkley, "Bootstrap Methods and Their Application," Cambridge Univ. Press (1997), pp. 358-362, using 1000 re-samplings of original data.

[0073] Because of the sparseness of samples in which PAA equaled or exceeded 500 μg/mL, 400 μg/mL proved to be a more stable and predictable target (i.e. high) value. Of the three categorizations of ratio considered, the cutpoint of 2.5 was the best discriminator and predictor of the risk of experiencing an high value. For example, referring to Table 3, a subject with a PAA:PAGN ratio > 2.5 at t=12 hours after dosing has a 36.4% chance (95% c. i.= 0.125, 0.752) of exceeding 400 μg/mL in PAA sometime during the 24-hour PK sampling period.

[0074] Results were similar whether the ratio was computed from plasma drawn at pre-dose, 12 hours after initiation of dosing, or the maximum ratio encountered anytime between pre-dose and 12 hours after initiation of dosing.

[0075] Due to the very high intra-day variability of plasma PAA levels, a PAA:PAGN ratio observed as exceeding 2.0 at a certain time following dosing may not remain greater than 2.0 in subsequent times. To evaluate the optimal time for obtaining a PAA:PAGN ratio measurement (i.e., the time that gives the greatest probability of correctly detecting a subject whose PAA:PAGN ratio ever equals or exceeds 2.0 during the dosing period), ratios were evaluated at 0 (pre-dose) and 2, 4, 6, 8, 10, and 12 hours post-dosing and modeled using GEE methodology. Pairwise differences in sensitivity between time points were evaluated using LS means and confidence intervals were computed.

[0076] Figure 3 plots the estimated probabilities of correctly detecting a ratio profile that ever equals of exceeds 2.0. With the exception of time= 2 hours and time=10 hours, time points of 0, 4, 6, 8, and 12 hours post-dosing were equally effective in detecting subjects who equal or exceed a PAA:PAGN ratio of 2.0 at some point during the dosing period. Sensitivities were in the range of 75-90 percent. There were too few blood samples collected at t=10 hours to analyze inter-time differences. Differences in predictive value were observed. For example, blood samples collected at t= 2 hours post-dosing had a significantly lower probability of detecting subjects who equal or exceed a PAA:PAGN ratio of 2.0 than samples collected at t=0 (p = 0.036), 4 (p = 0.032), or 6 hours (p = 0.017) post-dosing (p values are comparisons of t=2 hour probability with other time points). Similarly, a sample collected at t=12 hours following initiation of dosing had the highest probability (87%) of detecting a subject whose ratio ever equals or exceeds 2.0. However, for

practical clinical purposes, the differences in predictive value among time points was trivial relative to the dramatically greater variability in PAA values themselves, meaning that random blood draws can be used for measurement of PAA:PAGN ratio.

[0077] Further exploration of the fluctuation of PAA:PAGN ratios over time was conducted by dividing the subject population into cohorts according to the maximum PAA:PAGN ratio achieved during the 24-hour PK sampling time during the dosing period. Cohorts were divided into "low" (maximum ratio <= 2.0), "medium" (maximum ratio: 2.01-2.50), and "high" (maximum ratio > 2.50). Each cohort was then followed over time during the dosing period at t= 0 hours(pre-dose), 4, 6, and 8 hours post-dosing and the distribution of PAA:PAGN ratios within the cohort summarized using a box-and-whisker plot at each time point. This analysis was conducted for the PK-timepoint-specific population as a whole (analysis population B) as well as for each disease subpopulation separately.

[0078] Figure 4 plots the progression of ratios for all subjects combined. Each "panel" of the plot that divides the graphing space into thirds represents one cohort. Subjects in the high cohort had high ratios throughout the day and not only at a particular time point. Therefore, subjects in this cohort (n=73 subject/dosing periods) started with high ratios (median ratio > 2.5) and remained high throughout the first 12 hours. This finding is consistent with the findings plotted in Figure 3 which revealed the consistency of sensitivity in ratios.

[0079] The relationship between PAA levels and PAA:PAGN ratios was further analyzed by categorizing ratios into "low" (maximum ratio <= 2.0), "medium" (maximum ratio: 2.01-2.50), and "high" (maximum ratio > 2.50). Unlike the previous analysis, this analysis did not associate subject/dosing periods with particular cohorts (i.e., all samples and all time points are combined with regard to the subject or dosing period).

[0080] Figure 5A shows the box-and-whisker plots of PAA levels grouped by the above categories of PAA:PAGN ratio for all subjects, while Figure 5B shows the same for UCD and HE subjects only. The results were very similar in both analysis sets. Following a statistically significant overall Kruskal-Wallis test ($p < 0.0001$), pairwise comparisons of PAA levels were conducted using Wilcoxon-Mann-Whitney with a Bonferroni alpha correction of (0.0167). In both analysis sets, ratios greater than 2.5 had significantly higher PAA levels ($p < 0.001$) than either

ratios between 2.0 – 2.5 or ratios less than 2.0. Furthermore, ratios between 2.0 – 2.5 were associated with significantly higher PAA levels than ratios less than 2.0 ($p < 0.001$).

Example 2: Analysis of PAA:PAGN ratio as a guide to dose adjustment and monitoring in a UCD patient:

[0081] Patient 1 was a 15 year old partial OTC female receiving HPN-100 as maintenance therapy for her UCD at a dose of 9 mL/day. The patient's ammonia had been controlled since her last routine visit around 6 months ago, but she was complaining of headache and lack of appetite for the past 3 days. Ammonia and metabolite levels were tested after overnight fasting and showed the following results: ammonia 55 μmol/L, PAA and PAGN below levels of quantification. The physician suspected non-compliance with drug and repeated the tests in midday several hours after lunch and found the following results: ammonia: 117 μmol/L; PAA 55 μg/L, PAGN 121 μg/L, and PAA:PAGN ratio approximately 0.5. The patient indicated that she had been fully compliant with her medication. Based on the PAA to PAGN ratio of 0.5 and ammonia of 117, the physician decided to increase the dosage of HPN-100 to 12 mL/day. After one week of treatment with the new dose of HPN-100, all symptoms resolved and the laboratory tests after overnight fasting showed the following: ammonia 9 μmol/L; PAA 12.9 μg/L, PAGN of 9 μg/L, and PAA:PAGN ratio of 1.3. Midday tests showed the following: ammonia 35 μmol/L, PAA 165 μg/L, PAGN 130 μg/L, and PAA:PAGN ratio of ~1.2. The patient was considered controlled and the dose remained at 12 mL/day.

Example 3: Analysis of PAA:PAGN ratio as a guide to dose adjustment in a UCD patient:

[0082] Patient 2 was a 1 year old male OTC receiving 600 mg/kg of NaPBA per day. The patient presented with poor feeding and somnolence. Laboratory tests showed ammonia levels of <9 μmol/L, PAA levels of 530 μg/L, PAGN levels of 178 μg/L, and a PAA:PAGN ratio of >2.5, suggesting that the dose of NaPBA was greater than the patient could effectively convert to PAGN. The treating physician decided to decrease the dose of NaPBA to 450 mg/Kg/day. After one week of treatment with the new dosage, the patient's mother reported that he was eating well and was no longer somnolent. Laboratory tests showed the following: ammonia 20 μmol/L, PAA 280 μg/L, and PAGN 150 μg/L.

Example 4: Analysis of PAA:PAGN ratio as a guide to assessment of importance of a high PAA level in a UCD patient:

[0083] Patient 3 is a 25 year old OTC female who is being treated with HPN-100. The physician had to increase the dose of HPN-100 several times in order to achieve clinical and blood ammonia within normal limits. Patient 3 was treated at a dose of 18 mL/day for her UCD for the past month. In her next office visit, she did not have any complaints and the following lab results were reported: ammonia 22 μmol/L, PAA 409 μg/L, PAGN 259 μg/L, and PAA:PAGN ratio of 1.5. Despite the patient's relatively high PAA levels, the PAA:PAGN ratio indicated that the subject was being adequately treated and that the patient was able to effectively metabolize the high dose of HPN-100 that she was receiving. The physician decided to continue the treatment as planned.

Example 5: Analysis of PAA:PAGN ratio as a guide to dose adjustment in a patient with spinal muscular atrophy and concomitant liver disease:

[0084] Patient 4 was a 2 year old female being treated with a liquid form of NaPBA for her type II SMA. The patient also suffered from chronic hepatitis C virus infection acquired perinatally from her infected mother. The patient had been having mild to moderate elevation of transaminases since birth, with episodes of icterus and a recent liver biopsy has confirmed presence of chronic hepatitis and cirrhosis. The patient was receiving 4 g of NaPBA per day, and the physician wanted to increase the dosage due to the patient's growth but was concerned about the effects of liver dysfunction on drug metabolism. The physician ordered plasma PAA and PAGN levels and the results were as follows: PAA 110 μg/L, PAGN 85 μg/L, PAA:PAGN ratio of 1.2. The physician decided to increase the dosage of NaPBA to 6 g/day, and repeated the plasma metabolite level measurements after one week of treatment with the new regimen. The results were as follows: PAA 155 μg/L, PAGN 110 μg/L, and PAA:PAGN ratio of 1.4. The physician decided to leave the patient on 6 g/day of NaPBA since his liver seems to have adequate capacity to metabolize 6 g of NaPBA.

Example 6: Analysis of PAA:PAGN ratio as a guide to dose adjustment in a patient with Huntington's Disease and concomitant liver disease:

[0085] Patient 5 was a 56 year old male diagnosed with Huntington's disease several years ago. He also had a history of alcohol abuse and was diagnosed with alcoholic cirrhosis last year. His

wife enrolled him in clinical trials that involved an experimental drug delivering PBA at a slow rate, thereby enabling once-a-day dosing of the drug. The study had an option for dose escalation after 2 weeks of treatment if clinically safe. Although the protocol did not exclude patients with liver dysfunction, the investigator was concerned about PBA metabolism and possible accumulation of PAA in higher doses due to the patient's liver dysfunction. The investigator enrolled the patient in the low dose group and performed plasma PBA, PAA and PAGN measurements after 6 weeks of treatment with experimental drug. The patient reported improvement in his HD symptoms with no specific complains. Plasma metabolite levels after six weeks of treatment were as follows: PBA 45 μg/L; PAA 159 μg/L, and PAGN 134 μg/L. The dosage of the drug was increased by 50%. After four days of treatment at the new dosage, the patient started to complain about short episodes of somnolence. The investigator performed a blood test and observed the following: PBA 44 μg/L; PAA 550 μg/L, PAGN 180 μg/L, and PAA:PAGN ratio of >3. The PAA:PAGN ratio of greater than 2.5 indicated that the patient's liver could not effectively metabolize the higher dose of the drug, and the investigator therefore decided to reduce the dosage of the experimental drug and not continue dose escalation.

Example 7: Analysis of PAA:PAGN ratio as a guide to dose adjustment in a patient with MSUD:

[0086] Patient 6 was a 4 year old female being treated with HPN-100 for MSUD. The patient was receiving 6 mL of HPN-100 once a day, and the physician wanted to increase the dosage due to the patient's growth. Midday plasma PAA and PAGN measurements after the dose of medication were as follows: PAA 550 μg/L, PAGN 180 μg/L, and PAA:PAGN ratio of >2.5. The physician believed a lower dosage of HPN-100 would not be as effective for the patient, and decided to change the dosing regimen to 3 mL BID instead of 6 mL QD based on the high PAA:PAGN ratio. The tests were repeated after one week of treatment with the new BID regimen, with the following results: PAA 350 μg/L, PAGN 190 μg/L, and PAA:PAGN ratio of 1.8. Based on the ratio of 1.8, the physician decided to leave the patient on 3 mL BID since she can efficiently use a total dose of 6 mL/day given in divided doses but not as a bolus.

Example 8: Analysis of PAA:PAGN ratio as a guide to monitor a patient with HE and hepatic impairment:

[0087] Patient 7 was a 55 year old Caucasian male diagnosed with alcoholic cirrhosis 3 years ago. His transaminase levels had been mildly elevated and he had recently experienced mild episodes of HE. In the last assessment at the time of hospital admission for a grade 2 HE episode, the patient had a blood ammonia of 85 μmol/L, ALT of 55 U/L, and AST of 47 U/L, and a calculated MELD score of 11. The physician decided to start an ammonia scavenging therapy for the patient and treated him with HPN-100 6 mL BID. The patient returned for a follow up visit after 3 months, during which time he had experienced no episodes of HE. His laboratory assessments showed the following: ammonia of 30 μmol/L, plasma PAA level of 285 μg/mL, PAGN level of 120 μg/L, ALT of 66 U/L, AST of 50 U/L, and calculated MELD score of 13. The physician suspected that the patient's hepatic function may be deteriorating and was concerned about possible accumulation of PAA. She calculated the ratio of PAA to PAGN as 2.4, and confirmed that the patient had not experienced any unusual symptoms such as dizziness, headache, or nausea. Considering patient's ammonia control, lack of specific side effects, and clinical remission, the physician decided not to change the dose and to see the patient in two weeks to repeat the laboratory tests. The physician also warned the patient to call her immediately if he experienced any of these symptoms. In two weeks, the patient's laboratory assessments were essentially unchanged from the previous visit, with a PAA to PAGN ratio of 2.3, and the patient did not report any unusual symptoms. Based on the PAA:PAGN ratio of less than 2.5, the physician decided to continue dosing with 6 mL BID of HPN-100 until the next routine visit.

Example 9: Analysis of PAA:PAGN ratio as a guide to monitoring treatment in a patient with Parkinson's Disease:

[0088] HPN-100 treatment was initiated at a dose of 4mL twice a day in a patient with Parkinson's Disease to produce target circulating levels of PAA expected to produce clinical benefit. After one week of treatment, the patient's circulating PAA level of 50 μg/mL was below the target range, and the PAA:PAGN ratio was determined to be 0.9. The physician concluded that the HPN-100 dose could be safely adjusted upward, and the dose was increased by 50% to 6 mL BID. The PAA level and PAA/PAGN ratio one week later were found to be 75 μg/mL and 1.4,

respectively. Since 75 μg/mL was still below the therapeutic PAA target level and the PAA:PAGN ratio of 1.4 indicated that conversion of PAA to PAGN had not been saturated, the patient's dosage was increased again by 50% to 9 mL BID. One week later, the patient's PAA and PAA:PAGN ratio were found to be 159 μg/mL and 2.6, respectively. Since the target PAA level was now approximately therapeutic but the PAA:PAGN ratio indicated that PAA to PAGN conversion was approaching saturation, HPN-100 dosage was decreased to 8 mL BID, at which time the patient's circulating PAA level was determined to be close to the target range and his PAA:PAGN ratio was determined to be 2. The patient's dose was not further adjusted and he continued to be monitored.

[0089] As stated above, the foregoing is merely intended to illustrate various embodiments of the present invention. The specific modifications discussed above are not to be construed as limitations on the scope of the invention. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of the invention, and it is understood that such equivalent embodiments are to be included herein. All references cited herein are incorporated by reference as if fully set forth herein.

REFERENCES

1. Brahe Eur J Hum Genet 13:256 (2005)
2. Bruneti-Pieri Human Molec Genet 20:631 (2011)
3. Brusilow Science 207:659 (1980)
4. Brusilow Pediatr Res 29:147 (1991)
5. Brusilow Metabolism 42:1336 (1993)
6. Chung Clin Cancer Res 6:1452 (2000)
7. Cudkowicz ALS 10:99 (2009)
8. Hines Pediatr Blood Cancer 50:357 (2008)
9. Hogarth Mov Disord 22:1962 (2007)
10. Lee Mol Genet Metab 100:221 (2010)
11. Lichter Mol Genet Metab 103:323 (2011)
12. McGuire Hepatology 51:2077 (2010)
13. Mercuri Neuromuscul Disord 14:130 (2004)
14. Mokhtarani Mol Genet Metab 105:342 (2012)

15. Moldave J Biol Chem 229:463 (1957)
16. Monteleone Mol Genet Metab 105:343 (2012)
17. Ong Am J Med 114:188 (2003)
18. Perrine Pediatr Ann 37:339 (2008)
19. Ryu J Neurochem 93:1087 (2005)
20. Thiebault Cancer Res 54:1690 (1994)
21. Thiebault Cancer 75:2932 (1995)

What is claimed is:

1. A method of treating a nitrogen retention disorder in a subject comprising:

(a) administering a first dosage of a PAA prodrug,

(b) measuring plasma PAA and PAGN levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the PAA prodrug based on the determination in (d).

2. A method of treating a nitrogen retention disorder in a subject who has previously been administered a first dosage of a PAA prodrug comprising:

(a) measuring plasma PAA and PAGN levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the first PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(d) administering a second dosage of the PAA prodrug based on the determination in (c).

3. A method of treating a condition for which PAA prodrug administration is expected to be beneficial in a subject comprising:

(a) administering a first dosage of a PAA prodrug,

(b) measuring plasma PAA and PAGN levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the PAA prodrug based on the determination in (d).

4. A method of treating a condition for which PAA prodrug administration is expected to be beneficial in a subject who has previously been administered a first dosage of a PAA prodrug comprising:

(a) measuring plasma PAA and PAGN levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the first PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(d) administering a second dosage of the PAA prodrug based on the determination in (c).

5. A method of adjusting the dosage of a PAA prodrug comprising:

(a) administering a first dosage of a PAA prodrug,

(b) measuring plasma PAA and PAGN levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the PAA prodrug based on the determination in (d).

6. A method of optimizing the therapeutic efficacy of a PAA prodrug in a subject who has previously been administered a first dosage of a PAA prodrug comprising:

(a) measuring plasma PAA and PAGN levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the PAA prodrug as necessary based on the determination in (c).

7. The method of claim 1 or 2, wherein the nitrogen retention disorder is selected from the group consisting of UCD, HE, and ESRD.

8. The method of claim 3 or 4, wherein the disorder is selected from the group consisting of cancer, a neurodegenerative diseases, a metabolic disorder, and sickle cell disease.

9. The method of any of claims 1-6, wherein the target range is 1 to 2.5.

10. The method of any of claims 1-6, wherein the target range is 1 to 2.

11. The method of any of claims 1-6, wherein measurement of PAA and PAGN levels is carried out after the first dosage of PAA prodrug has had sufficient time to reach steady state.

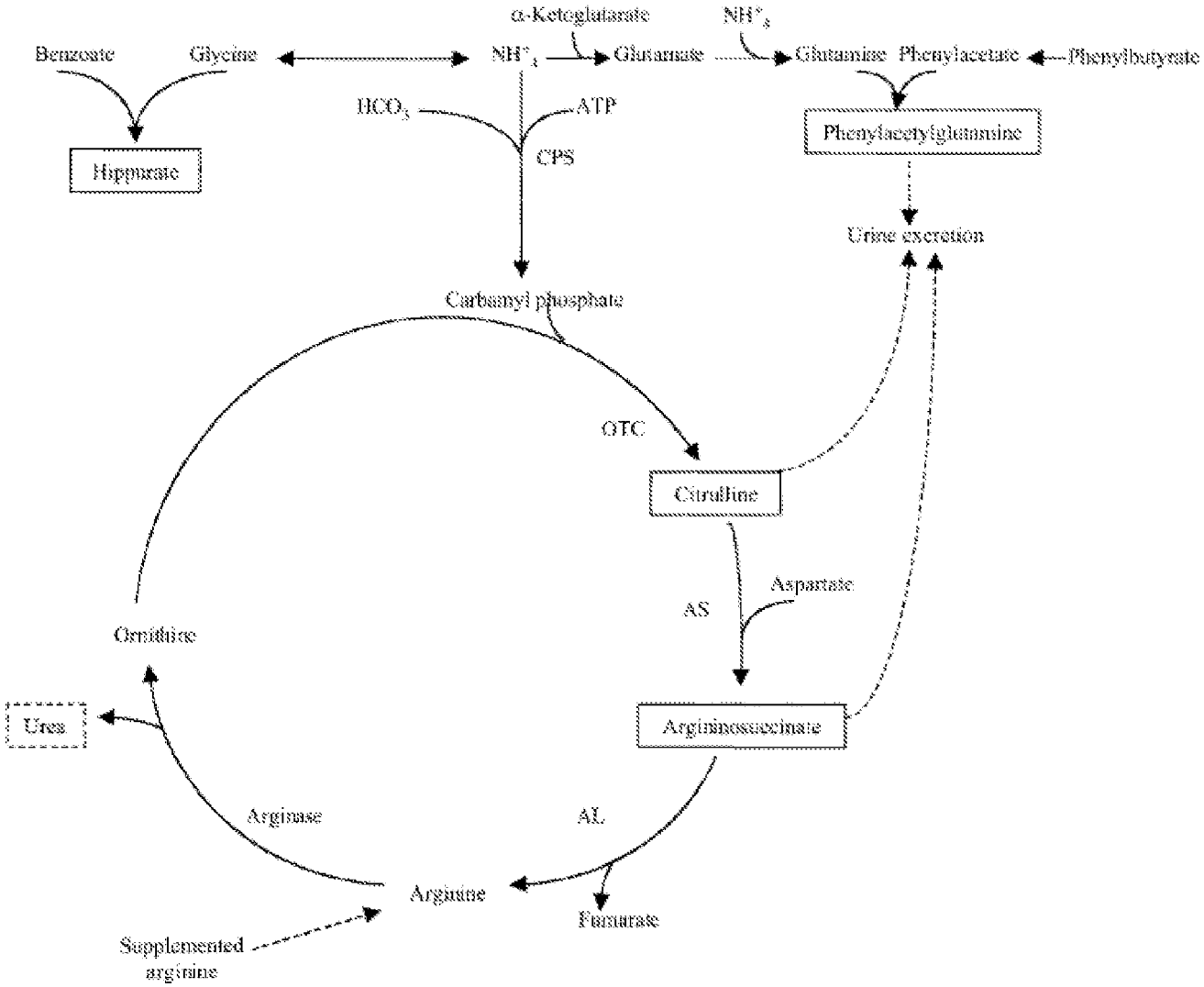
12. The method of claim 11, wherein measurement of PAA and PAGN levels is carried out 48 hours to 1 week after the first dosage of PAA prodrug is administered.

13. The method of any of claims 1-6, wherein the PAA prodrug is selected from the group consisting of NaPBA and HPN-100.

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.

Figure 1


α-Ketoglutarate
NH^+_3
Benzoate
Glycine
NH^+_3
Glutamate
Glutamine
Phenylacetate
Phenylbutyrate
HCO_3
ATP
CPS
Hippurate
Phenylacetylglutamine
Urine excretion
Carbamyl phosphate
OTC
Citrulline
Aspartate
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Ornithine
Urea
Argininosuccinate
Arginase
AL
Arginine
Fumarate
Supplemented arginine

Figure 2A

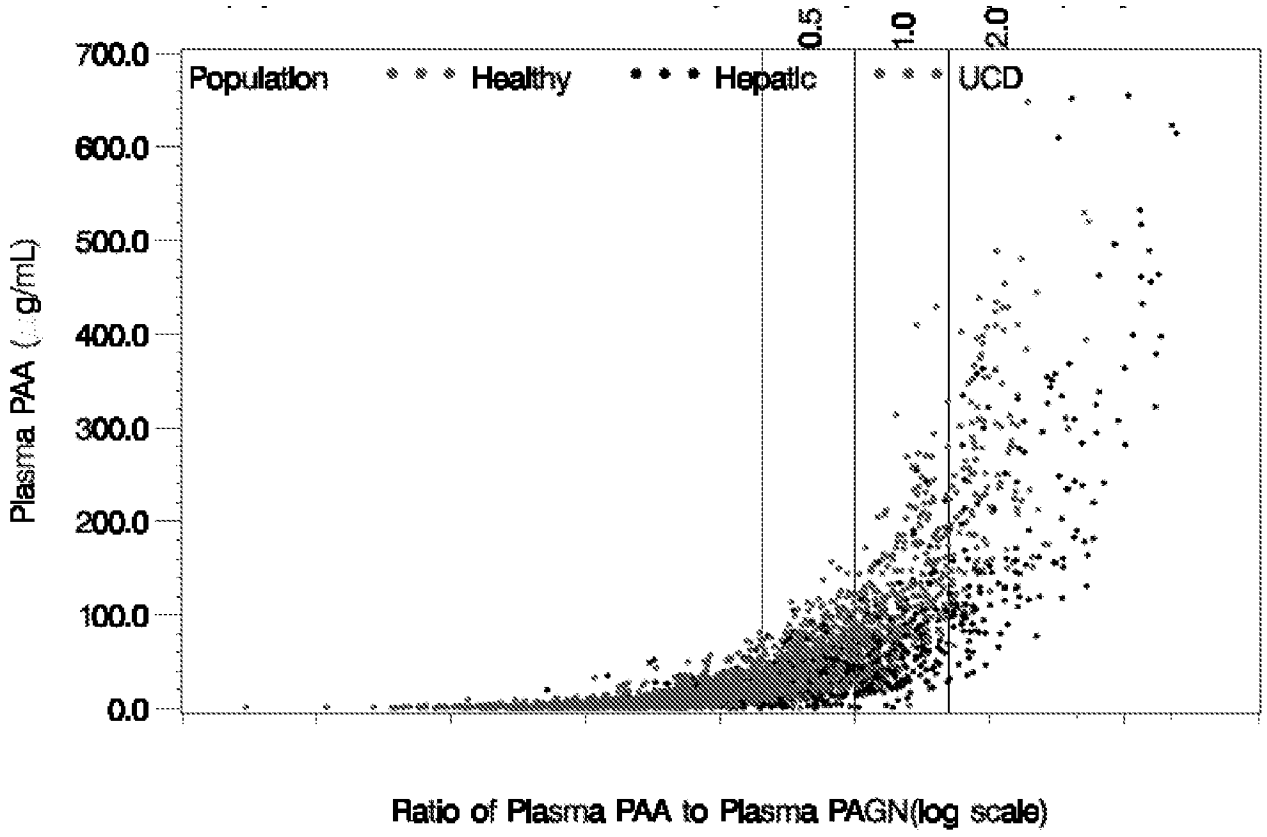

0.5
1.0
2.0
Population
Healthy
Hepatic
UCD
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0.0
Plasma PAA (μg/mL)
Ratio of Plasma PAA to Plasma PAGN(log scale)

Figure 2B

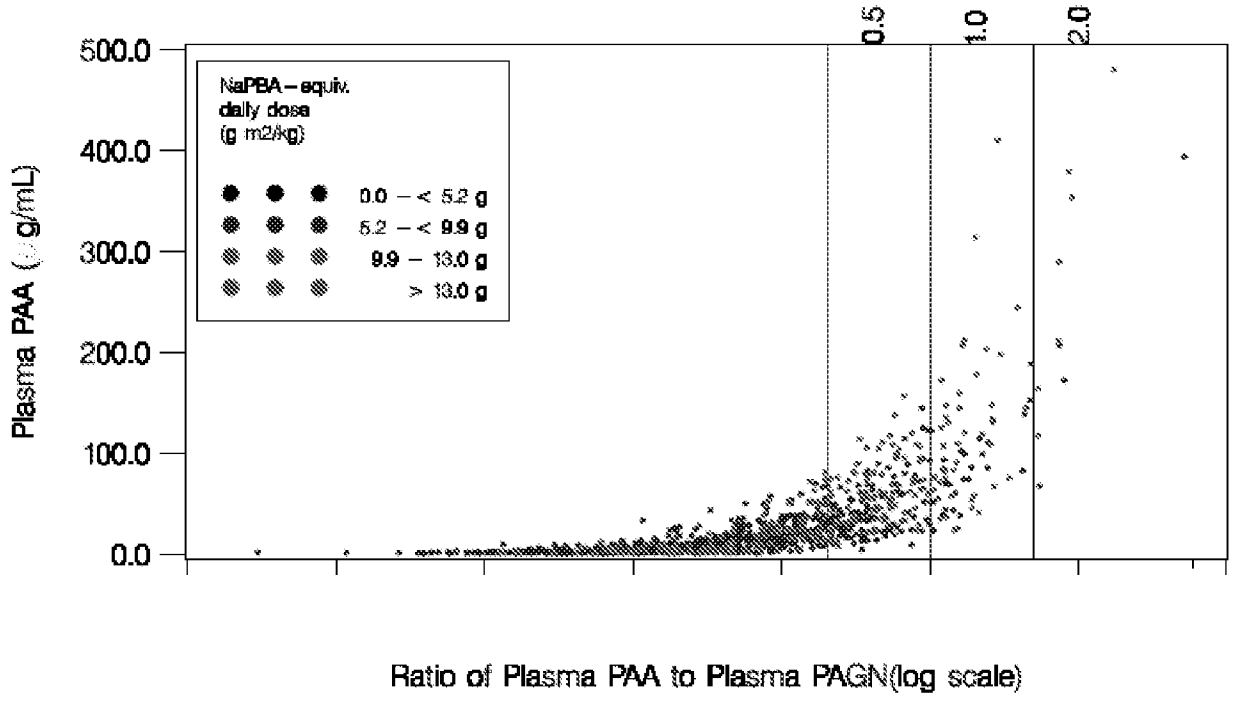

0.5
1.0
2.0
500.0
400.0
300.0
200.0
100.0
0.0
NaPBA – equiv.
daily dose
(g m2/kg)
0.0 – < 5.2 g
5.2 – < 9.9 g
9.9 – 13.0 g
> 13.0 g
Plasma PAA (µg/mL)
Ratio of Plasma PAA to Plasma PAGN(log scale)

Figure 2C

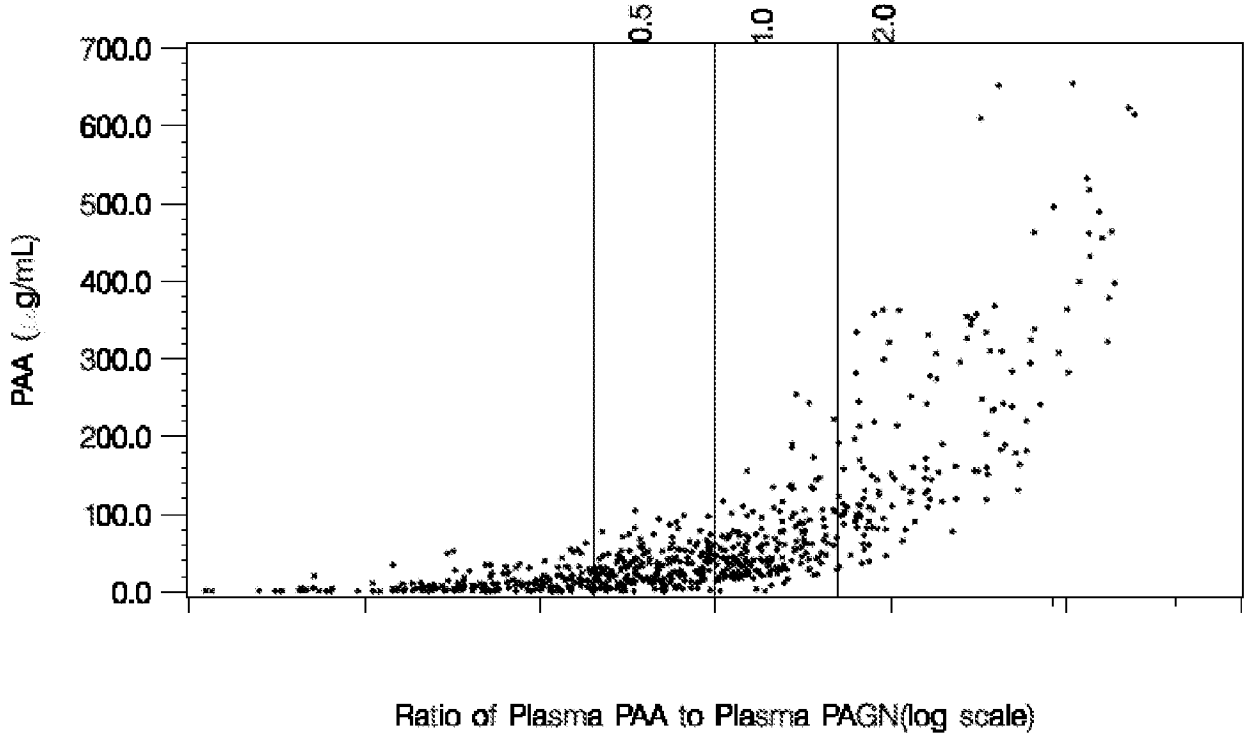
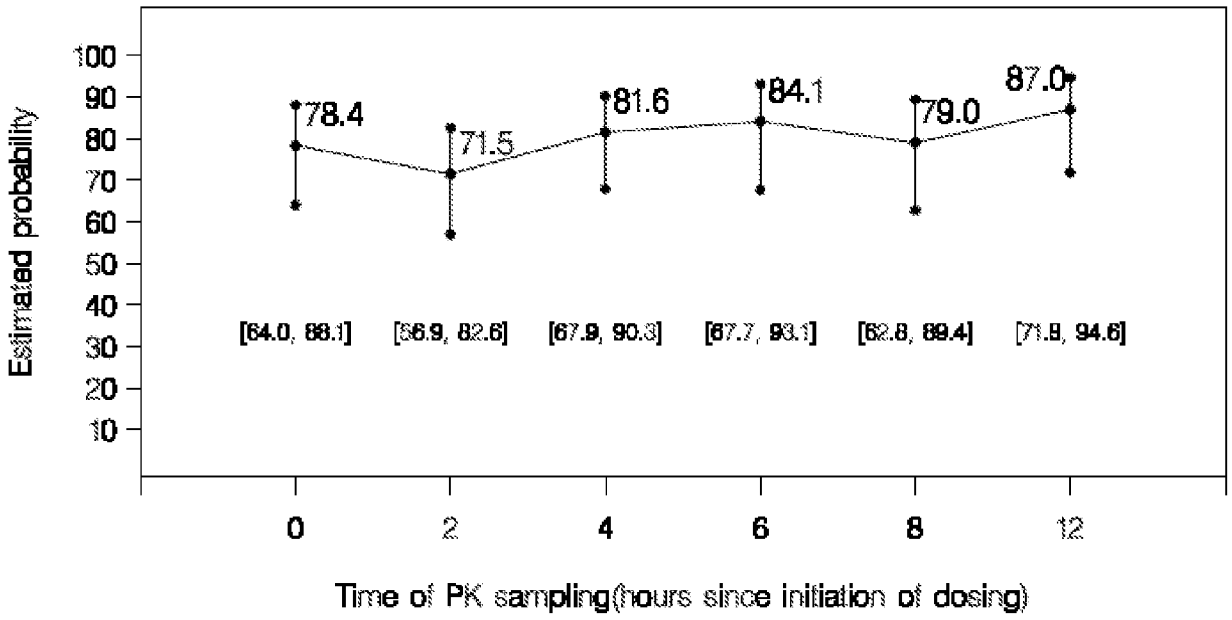

0.5
1.0
2.0
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0.0
PAA (µg/mL)
Ratio of Plasma PAA to Plasma PAGN(log scale)

Figure 3



t=2 hrs signif. less than t=0(p=0.036), t=4(p=0.032), and t=6(p=0.017)
No other time differences statistically significant. Time=10 omitted due to too few observations

Figure 4

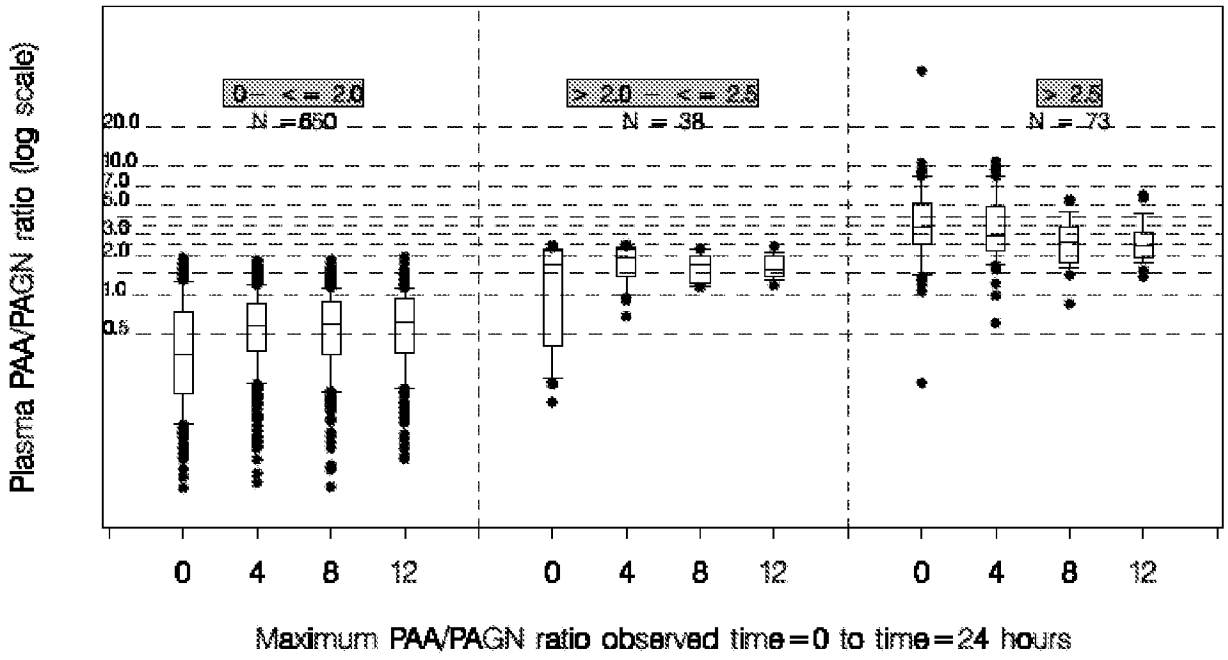

Plasma PAA/PAGN ratio (log scale)
0 < = 2.0
N = 650
> 2.0 < = 2.5
N = 38
> 2.5
N = 73
20.0
10.0
7.0
5.0
3.6
2.0
1.0
0.5
0
4
8
12
Maximum PAA/PAGN ratio observed time=0 to time=24 hours

Figure 5A

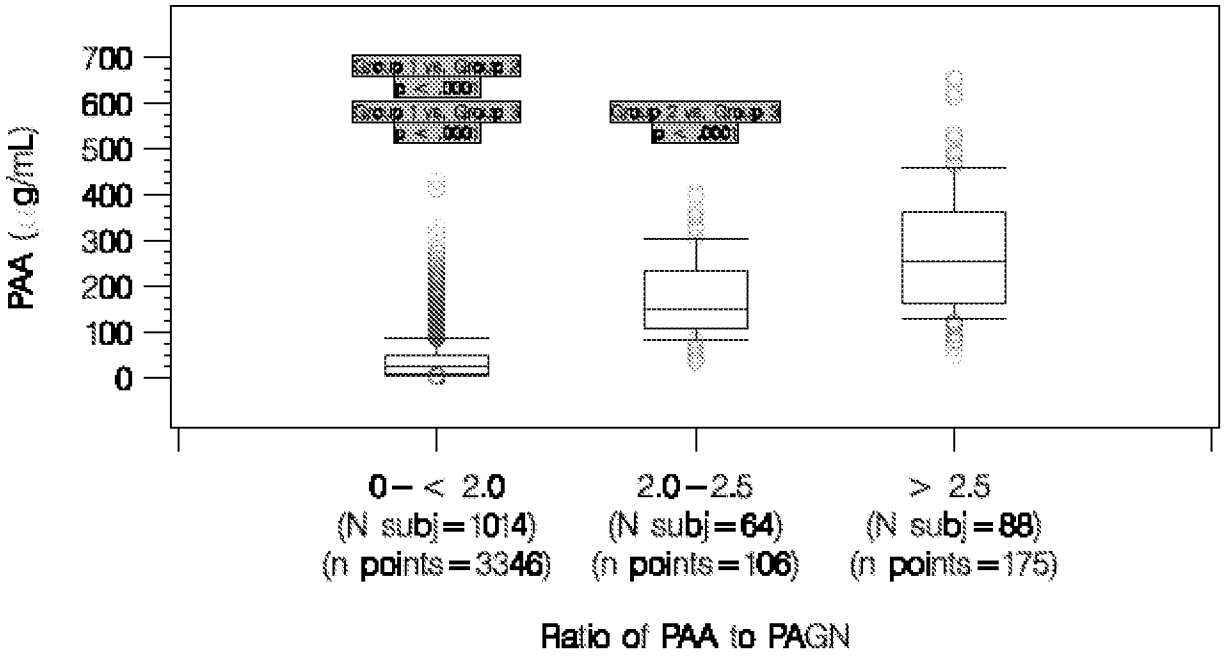
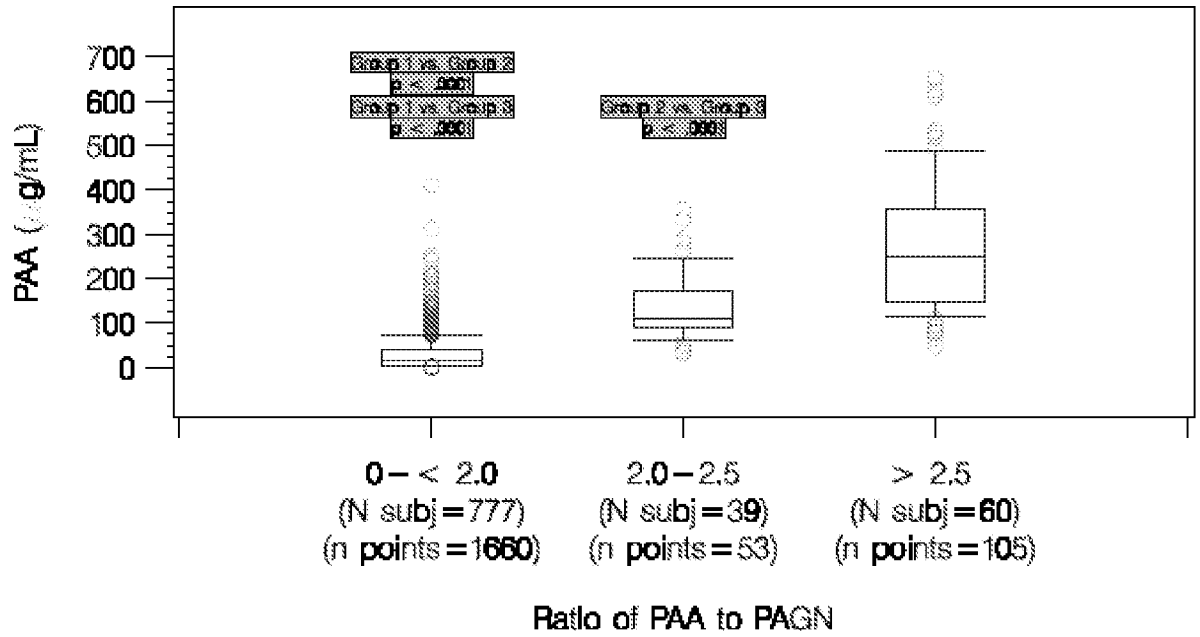


Figure 5B



Electronic Acknowledgement Receipt

EFS ID:	13716069
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce SCHARSCHMIDT
Customer Number:	34055
Filer:	Patrick D. Morris/Colleen Kirchner
Filer Authorized By:	Patrick D. Morris
Attorney Docket Number:	79532.8004.US01
Receipt Date:	11-SEP-2012
Filing Date:	
Time Stamp:	18:32:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

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2		US_Specification.pdf	421452 23dcf88e635702ec2320a497198d2dbec21cbf92	yes	52

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Specification	1	41
Claims	42	44
Abstract	45	45
Drawings-only black and white line drawings	46	52

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/610,580

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	95		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	310		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	125		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	40 minus 20 =	* 20	x 30 =	600	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	6 minus 3 =	* 3	x 125 =	375			
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MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				225			
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APPLICATION AS AMENDED - PART II

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

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
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13/610,580	09/11/2012	1765	0.00	79532.8004.US01	13	6

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Date Mailed: 09/26/2012

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Inventor(s)

Bruce Scharschmidt, Residence Not Provided;
Masoud Mokhtarani, Residence Not Provided;

Applicant(s)

Bruce Scharschmidt, Residence Not Provided;
Masoud Mokhtarani, Residence Not Provided;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/636,256 04/20/2012

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Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

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

Title

METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

Preliminary Class

528

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set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/610,580	09/11/2012	Bruce Scharschmidt	79532.8004.US01

CONFIRMATION NO. 1957

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

FORMALITIES LETTER

OC000000056731559

Date Mailed: 09/26/2012

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**95** to complete the basic filing fee for a small entity.*
- The oath or declaration is missing.

A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.

Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of $ **1200** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- A surcharge (for late submission of the basic filing fee, search fee, examination fee or inventor's oath or declaration) as set forth in 37 CFR 1.16(f) of $ **65** for a small entity in compliance with 37 CFR 1.27, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $ **1795** for a small entity

- $ **95** Statutory basic filing fee.
- $ **65** Surcharge.
- The application search fee has not been paid. Applicant must submit $ **310** to complete the search fee.

- The application examination fee has not been paid. Applicant must submit $ **125** to complete the examination fee for a small entity in compliance with 37 CFR 1.27.
- Total additional claim fee(s) for this application is $ **1200**
  - $ **375** for **3** independent claims over 3.
  - $ **600** for **20** total claims over 20.
  - $ **225** for multiple dependent claim surcharge.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/rerry/

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

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
13610580	

Applicant(s) Bruce Scharschmidt

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
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Total Indep	6		0		0	
Total Depend	34	↵	0	↵	0	↵
Total Claims	40		0		0	

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	Indep	Depend	Indep	Depend	Indep	Depend
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPL. OF:	BRUCE SCHARSCHMIDT ET AL.	ART UNIT:	1765
APPLICATION NO.:	13/610,580	CONF. NO:	1957
FILED:	SEPTEMBER 11, 2012		
FOR:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS		

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Notice to File Missing Parts of Nonprovisional Application mailed on September 26, 2012, applicants submit the following:

☒ an executed Declaration of Inventorship;

☒ an executed Power of Attorney by Assignee; and

☒ a Preliminary Amendment.

1. Authorization for Extensions of Time Under 37 C.F.R. § 1.136 (a)(3)

Applicants petition for an Extension of Time if necessary for timely filing of this Response. The Commissioner is authorized to treat this or any future reply requiring a Petition for Extension of Time under 37 C.F.R. § 1.136 (a)(3) for its timely submission as incorporating a petition herefore for the appropriate length of time. Please charge all required extension of time fees in this application to Deposit Account No. 50-2586.

2. Fee Calculation and Payment

For:	(Col. 1) No. Filed	(Col. 2) No. Extra	Small Entity			Other Than a Small Entity	
			Rate	Fee		Rate	Fee
Filing Fee			$95	$95.00	or	$380	$
Search Fee			$310	$310.00	or	$620	$
Examination Fee			$125	$125.00	or	$250	$
Total Claims	23 – 20	3	X $31=	$93.00	or	X $60=	$
Independent Claims	4 – 3	1	X $125=	$125.00	or	X $250=	$
☒ Multiple Dependent Claim Presented			+ $230=	$230.00	or	+ $450=	$
Application Size Fee – for each additional 50 sheets that exceeds 100 sheets			X $160=	$	or	X $310=	$
Missing Parts Surcharge			$65.00	$65.00		$130	$
Extension of Time Fee				$			$
*If the difference in Col. 1 is less than zero, enter "0" in Col. 2.			TOTAL	$1043.00	or	TOTAL	**$**

☒ Please charge Deposit Account No. 50-2586 in the amount of $1,043.00 for the requisite fees.

☒ Please charge any deficiency or credit to Deposit Account No. 50-2586.

Dated: November 21, 2012

Respectfully submitted,

PERKINS COIE LLP

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

Correspondence Address:
Customer No. 34055
Perkins Coie LLP
Patent - LA
P.O. Box 1208
Seattle, WA 98111-1208
Phone: (310) 788-9900
Fax: (206) 332-7198

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPL. OF: BRUCE SCHARSCHMIDT ET AL.	ART UNIT: 1765
APPLICATION NO.: 13/610,580	CONF. NO: 1957
FILED: SEPTEMBER 11, 2012	
FOR: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS	

PRELIMINARY AMENDMENT

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

Sir:

Prior to examination on the merits, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims beginning on page 2.

Conclusion begins on page 5.

[Continued on next page.]

AMENDMENTS TO THE CLAIMS

The following is a complete listing of the claims pending in the application, as amended:

1. (original) A method of treating a nitrogen retention disorder in a subject comprising:

(a) administering a first dosage of a PAA prodrug,

(b) measuring plasma PAA and PAGN levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the PAA prodrug based on the determination in (d).

2. (original) A method of treating a nitrogen retention disorder in a subject who has previously been administered a first dosage of a PAA prodrug comprising:

(a) measuring plasma PAA and PAGN levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the first PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(d) administering a second dosage of the PAA prodrug based on the determination in (c).

3. (canceled)

4. (canceled)

5. (original) A method of adjusting the dosage of a PAA prodrug comprising:

(a) administering a first dosage of a PAA prodrug,

(b) measuring plasma PAA and PAGN levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the PAA prodrug based on the determination in (d).

6. (original) A method of optimizing the therapeutic efficacy of a PAA prodrug in a subject who has previously been administered a first dosage of a PAA prodrug comprising:

(a) measuring plasma PAA and PAGN levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the PAA prodrug as necessary based on the determination in (c).

7. (original) The method of claim 1 or 2, wherein the nitrogen retention disorder is selected from the group consisting of UCD, HE, and ESRD.

8. (canceled)

9. (currently amended)The method of any of claims 1[[-]], 2, 5, or 6, wherein the target range is 1 to 2.5.

10. (currently amended)The method of any of claims 1[[-]], 2, 5, or 6, wherein the target range is 1 to 2.

11. (currently amended)The method of any of claims 1[[-]], 2, 5, or 6, wherein measurement of PAA and PAGN levels is carried out after the first dosage of PAA prodrug has had sufficient time to reach steady state.

12. (original) The method of claim 11, wherein measurement of PAA and PAGN levels is carried out 48 hours to 1 week after the first dosage of PAA prodrug is administered.

13. (currently amended)The method of any of claims 1[[-]], 2, 5, or 6, wherein the PAA prodrug is selected from the group consisting of NaPBA and HPN-100.

CONCLUSION

Applicant respectfully requests consideration of the application in view of this preliminary amendment. If the Examiner has any questions or matters that can be expediently handled by telephone, he or she is encouraged to contact the undersigned at (310) 788-9900.

Respectfully submitted,
Perkins Coie LLP

Date: November 21, 2012

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

Correspondence Address:
Customer No. 34055
Perkins Coie LLP
Patent – LA
P.O. Box 1208
Seattle, WA 98111-1208
Phone: (310) 788-9900
Fax: (206) 332-7198

UTILITY DECLARATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS**, the specification of which

(Check One) ☐ is attached hereto OR
☒ was deposited on September 11, 2012 and accorded United States Application No. 13/610,580.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Date of Filing	Priority Claimed Yes	Priority Claimed No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date
61/636,256	April 20, 2012

I hereby claim the benefit under Title 35, United States Code § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date	Status-Patented, Pending or Abandoned

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

201	FULL NAME OF INVENTOR	FIRST Name: Bruce	MIDDLE Initial:	LAST Name: SCHARSCHMIDT	
	RESIDENCE & CITIZENSHIP	City: San Francisco	State or Foreign Country: CA	Country of Citizenship: USA	
	POST OFFICE ADDRESS	45 St. Francis Boulevard	City: San Francisco	State or Country: CA	Zip Code: 94127

INVENTOR'S SIGNATURE Bruce J. Scharschmidt DATE November 9 2012

201	FULL NAME OF INVENTOR	FIRST Name: Masoud	MIDDLE Initial:	LAST Name: MOKHTARANI	
	RESIDENCE & CITIZENSHIP	City: Walnut Creek	State or Foreign Country: CA	Country of Citizenship: USA	
	POST OFFICE ADDRESS	725 Castle Rock Road	City: Walnut Creek	State or Country: CA	Zip Code: 94598

INVENTOR'S SIGNATURE M. Mok DATE 11/9/2012

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: BRUCE SCHARSCHMIDT ET AL.	CONFIRMATION NO.: 1957
APPLICATION NO.: 13/610,580	ART UNIT: 1765
FILING DATE: SEPTEMBER 11, 2012	
FOR: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS	

Power of Attorney by Assignee and Certification Under 37 C.F.R. § 3.73(b)

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

Sir:

I, the undersigned, acting on behalf of the Assignee of the entire right, title and interest in the above-identified patent application, by virtue of an Assignment attached hereto appoint the attorneys and agents listed below to prosecute this patent and transact all business with the U.S. Patent and Trademark Office in connection therewith. This appointment is to the exclusion of the inventor(s) and their attorney(s) and agent(s) in accordance with the provisions of 37 C.F.R. § 3.71.

All prior powers of attorney for this application are hereby revoked. The Assignee hereby appoints all of the registered practitioners identified by Customer Number 34055:

Customer Number 34055
Perkins Coie LLP
Patent – LA
P.O. Box 1208
Seattle, WA 98111-1208
Phone: (310) 788-9900
Fax: (206) 332-7198

Please direct all inquires to Patrick D. Morris at the above Customer Number.

In accordance with 37 C.F.R. § 3.73(b), I hereby certify that I am empowered to act on behalf of the Assignee. To the best of my knowledge and belief, title is in the Assignee, as evidenced by the Assignment noted above.

I further declare 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 Title 18, USC § 1001 and that such willful false statements may jeopardize the validity of this patent.

ASSIGNEE: HYPERION THERAPEUTICS, INC.

Signature: [signature]

Typed Name: Jeff Farrow

Title: CFO

Date: 11/9/12

Address: 601 Gateway Blvd., Suite 200, South San Francisco, CA 94080

ASSIGNMENT

THIS ASSIGNMENT is by Bruce SCHARSCHMIDT and Masoud MOKHTARANI (hereinafter collectively referred to as "Assignors"). Assignors have invented one or more certain inventions described in a United States Utility Patent Application entitled **METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS** (the "Application"), which was filed on September 11, 2012, as Application No. 13/610,580 (the "Invention(s)").

HYPERION THERAPEUTICS, INC., a corporation of the State of Delaware having a principal place of business at 601 Gateway Blvd., Suite 200, South San Francisco, CA 94080 ("Assignee"), desires to acquire the entire right, title, and interest in and to the Invention(s) and the Application, and in and to any patents (collectively, "Patents") that may be granted for the Invention(s) in the United States or in any foreign countries.

For valuable consideration, the receipt and sufficiency of which we acknowledge, Assignors hereby sell, assign, and transfer to Assignee, its successors, legal representatives and assigns, the entire right, title, and interest in and to: the Invention(s), the Application, and any Patents; any divisions, continuations, and continuations-in-part of the Application; any reissues, reexaminations, or extensions of any and all Patents; the right to file foreign applications directly in the name of Assignee; and the right to claim priority rights deriving from the Application (collectively, the "Rights"). Assignors warrant that they are the sole owner of the Rights, and that the Rights are unencumbered. Assignors also agree to not sign any writing or do any act conflicting with this assignment and to sign all documents and do such additional acts

as Assignee deems necessary or desirable to perfect Assignee's enjoyment of the Rights; prepare and prosecute the Application or any other applications for Patents; conduct proceedings regarding the Rights, including any litigation or interference proceedings; or perfect or defend title to the Rights.

Assignors request the Commissioner of Patents to issue any Patent of the United States that may be issued on the Invention(s) to Assignee.

This Assignment may be executed in counterparts.

Assignors:

Date: November 9 2012

Bruce SCHARSCHMIDT

Date: Nov/9/2012

Masoud MOKHTARANI

Assignee:

Date: 11/9/12

By:
for HYPERION THERAPEUTICS, INC.

Electronic Patent Application Fee Transmittal

Application Number:	13610580
Filing Date:	11-Sep-2012
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Patrick D. Morris/Colleen Kirchner
Attorney Docket Number:	79532.8004.US01

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	98	98
Utility Search Fee	2111	1	310	310
Utility Examination Fee	2311	1	125	125
Pages:				
Claims:				
Claims in excess of 20	2202	3	31	93
Independent claims in excess of 3	2201	1	125	125
Multiple dependent claims	2203	1	230	230

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous-Filing:				
Late filing fee for oath or declaration	2051	1	65	65
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1046**

Electronic Acknowledgement Receipt

EFS ID:	14290171
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	34055
Filer:	Patrick D. Morris/Colleen Kirchner
Filer Authorized By:	Patrick D. Morris
Attorney Docket Number:	79532.8004.US01
Receipt Date:	21-NOV-2012
Filing Date:	11-SEP-2012
Time Stamp:	14:10:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1046
RAM confirmation Number	2054
Deposit Account	502586
Authorized User	

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

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

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	8004US01_MPResponse.pdf	90992 f527355321e3724b34f4d0ba2fd74f161481e201	no	2
Warnings:					
Information:					
2		8004US01_PrelimAmendment.pdf	67028 4d61744ed56df1d491f8540297ff0b6780e8c2ff	yes	5

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	5

Warnings:					
Information:					
3	Oath or Declaration filed	8004US01_Declaration.pdf	570067 ad6ef309467e197cbf47f29944cd95668da9c172	no	2
Warnings:					
Information:					
4	Power of Attorney	8004US01_POA_Assignment.pdf	811694 0acd9fe7d3e40968cde46ea1e46930ce58861beb	no	4
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	41654 cafd151607d34ff082ff677a39c4c4c15f4bddec	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1581435		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronic Acknowledgement Receipt

EFS ID:	14290171
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	34055
Filer:	Patrick D. Morris/Colleen Kirchner
Filer Authorized By:	Patrick D. Morris
Attorney Docket Number:	79532.8004.US01
Receipt Date:	21-NOV-2012
Filing Date:	11-SEP-2012
Time Stamp:	14:10:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1046
RAM confirmation Number	2054
Deposit Account	502586
Authorized User	

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

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

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	8004US01_MPResponse.pdf	90992 f527355321e3724b34f4d0ba2fd74f161481e201	no	2
Warnings:					
Information:					
2		8004US01_PrelimAmendment.pdf	67028 4d61744ed56df1d491f8540297ff0b6780e8c2ff	yes	5

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	5

Warnings:					
Information:					
3	Oath or Declaration filed	8004US01_Declaration.pdf	570067 ad6ef309467e197cbf47f29944cd95668da9c172	no	2
Warnings:					
Information:					
4	Power of Attorney	8004US01_POA_Assignment.pdf	811694 0acd9fe7d3e40968cde46ea1e46930ce58861beb	no	4
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	41654 cafd151607d34ff082ff677a39c4c4c15f4bddec	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1581435		

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
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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/610,580	09/11/2012	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	11/21/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 25	Minus	** 40	= 0	X $31 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 3	Minus	***6	= 0	X $125 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	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))	*	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:
/CRYSTAL QUEEN/

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPL. OF:	BRUCE SCHARSCHMIDT ET AL.	ART UNIT:	1765
APPLICATION NO.:	13/610,580	CONF. NO:	1957
FILED:	SEPTEMBER 11, 2012		
FOR:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS		

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Notice to File Missing Parts of Nonprovisional Application mailed on September 26, 2012, applicants submit the following:

☒ an executed Declaration of Inventorship;

☒ an executed Power of Attorney by Assignee; and

☒ a Preliminary Amendment.

1. Authorization for Extensions of Time Under 37 C.F.R. § 1.136 (a)(3)

Applicants petition for an Extension of Time if necessary for timely filing of this Response. The Commissioner is authorized to treat this or any future reply requiring a Petition for Extension of Time under 37 C.F.R. § 1.136 (a)(3) for its timely submission as incorporating a petition herefore for the appropriate length of time. Please charge all required extension of time fees in this application to Deposit Account No. 50-2586.

11/29/2012 VVAN11 00000029 502586 13610580

01 FC:2202 93.00 DA

2. Fee Calculation and Payment

For:	(Col. 1) No. Filed	(Col. 2) No. Extra	Small Entity Rate	Small Entity Fee		Other Than a Small Entity Rate	Other Than a Small Entity Fee
Filing Fee			$95	$95.00	or	$380	$
Search Fee			$310	$310.00	or	$620	$
Examination Fee			$125	$125.00	or	$250	$
Total Claims	23 – 20	3	X $31=	$93.00	or	X $60=	$
Independent Claims	4 – 3	1	X $125=	$125.00	or	X $250=	$
☒ Multiple Dependent Claim Presented			+ $230=	$230.00	or	+ $450=	$
Application Size Fee – for each additional 50 sheets that exceeds 100 sheets			X $160=	$	or	X $310=	$
Missing Parts Surcharge			$65.00	$65.00		$130	$
Extension of Time Fee				$			$
*If the difference in Col. 1 is less than zero, enter "0" in Col. 2.			TOTAL	$1043.00	or	TOTAL	**$**

☒ Please charge Deposit Account No. 50-2586 in the amount of $1,043.00 for the requisite fees.

☒ Please charge any deficiency or credit to Deposit Account No. 50-2586.

Dated: November 21, 2012

Respectfully submitted,

PERKINS COIE LLP

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

Correspondence Address:
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UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/610,580	09/11/2012	Bruce Scharschmidt	79532.8004.US01

CONFIRMATION NO. 1957

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

POA ACCEPTANCE LETTER

OC000000057852953

Date Mailed: 12/04/2012

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/21/2012.

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.

/ltaba/

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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/610,580

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	98		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	310		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	125		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	26 minus 20 =	* 6	x 31 =	186	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1	x 125 =	125			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				230			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1074		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/610,580	09/11/2012	1765	1139	79532.8004.US01	10	4

CONFIRMATION NO. 1957

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

UPDATED FILING RECEIPT

OC000000057874784

Date Mailed: 12/04/2012

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

Inventor(s)

Bruce Scharschmidt, San Francisco, CA;
Masoud Mokhtarani, Walnut Creek, CA;

Applicant(s)

Bruce Scharschmidt, San Francisco, CA;
Masoud Mokhtarani, Walnut Creek, CA;

Power of Attorney: The patent practitioners associated with Customer Number 34055

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/636,256 04/20/2012

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 09/24/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/610,580**

Projected Publication Date: 10/24/2013

Non-Publication Request: No

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

Title

METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

Preliminary Class

528

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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

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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/610,580	09/11/2012	Bruce Scharschmidt	079532-8004.US01

CONFIRMATION NO. 1957

34055
PERKINS COIE LLP - LOS General
POST OFFICE BOX 1247
SEATTLE, WA 98111-1247

PUBLICATION NOTICE

OC000000064582275

Title:METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

Publication No.US-2013-0281530-A1
Publication Date:10/24/2013

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/610,580	09/11/2012	Bruce Scharschmidt	079532-8004.US01	1957

34055 7590 10/09/2014

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

EXAMINER	
TOWNSLEY, SARA ELIZABETH	
ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
10/09/2014	ELECTRONIC

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

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

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

patentprocurement@perkinscoie.com

Office Action Summary	Application No. 13/610,580	Applicant(s) SCHARSCHMIDT ET AL.	
	Examiner SARA E. TOWNSLEY	Art Unit 1629	AIA (First Inventor to File) Status No

-- 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 2 MONTHS 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 _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1,2,5-7 and 9-13* 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) _____ is/are rejected.

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

9)☒ Claim(s) *1, 2, 5-7, and 9-13* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

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

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Election of Species

1. This application contains claims directed to patentably distinct species. For initial search and examination purposes, Applicant is required to elect

- a single, distinct nitrogen retention disorder, e.g., UCD, as recited in claim 7; and
- a single, distinct PAA prodrug, e.g., HPN-100, as recited in claim 13.

Each of these species must be identified so as to yield one single, distinct method species (i.e., a single, distinct embodiment).

2. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1, 2, 5-7, and 9-13 are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement

may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. TOWNSLEY whose telephone number is 571-270-7672. The examiner can normally be reached on Mon-Fri from 9:00 am to 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff S. Lundgren, can be reached at 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SARA E. TOWNSLEY/
Examiner, Art Unit 1629

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13610580	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SARA E TOWNSLEY	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/05/2014								
	1	÷								
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	13	÷								

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **SCHARSCHMIDT, Bruce, et al.** **Serial No.:** 13/610,580 **Filed:** September 11, 2012 **For: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC PRODRUGS**		**Examiner:** TOWNSLEY, Sara Elizabeth **Group Art Unit:** 1629 **Docket No.:** 079532.8004.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 4th day of November 2014 via EFS-Web Electronic Filing. /Colleen Kirchner/ Colleen Kirchner

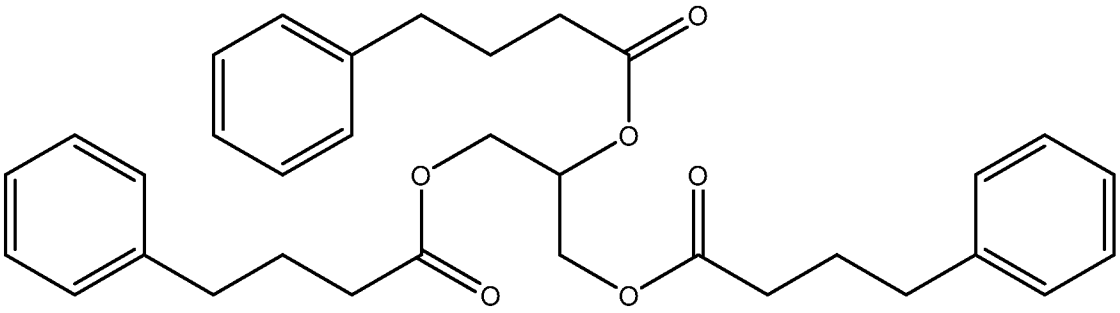
RESPONSE TO RESTRICTION REQUIREMENT

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

Sir:

The following is in response to the Restriction Requirement mailed October 9, 2014 for the above-identified application.

The Restriction Requirement requests that Applicants elect a single, distinct nitrogen retention disorder as recited in claim 7. Applicants elect urea cycle disorder (UCD) without traverse. The Restriction Requirement also requests that Applicants elect a single distinct PAA prodrug as recited in claim 13. Applicants elect glyceryl tri-[4-phenylbutyrate] (HPN-100) without traverse. HPN-100 has the following structure:



HPN-100 is a prodrug of phenylbutyrate (PBA) and a pre-prodrug of phenylacetic acid (PAA). As such, HPN-100 has the same active moiety as PBA and sodium PBA (i.e., PAA).

Pending claims 1, 2, 5-7, and 9-13 encompass the elected species.

If Applicants can do anything more to expedite this application, Applicants request that the Examiner contact the undersigned at (415) 344-7105.

Respectfully submitted,
Perkins Coie LLP

Date: November 4, 2014

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

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Perkins Coie LLP
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Facsimile: (206) 332-7198

Electronic Acknowledgement Receipt

EFS ID:	20606855
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	34055
Filer:	Lara J. Dueppen/Colleen Kirchner
Filer Authorized By:	Lara J. Dueppen
Attorney Docket Number:	079532-8004.US01
Receipt Date:	04-NOV-2014
Filing Date:	11-SEP-2012
Time Stamp:	18:33:28
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	Response to Election / Restriction Filed	8004US01_Response.pdf	88104 c1354e2a46aab48111b6acef1ad71575a1071c8f	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	88104

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO-1449 (Modified) (Use several sheets if necessary)				COMPLETE IF KNOWN	
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				First Named Inventor	SCHARSCHMIDT, Bruce
				Group Art Unit	1765
				Examiner Name	
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U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	U.S. Patent or Application NUMBER	Kind Code (if known)	Name of Patentee or Inventor of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	4,284,647 A		BRUSILOW	8/1981	
	A2	5,968,979		BRUSILOW	10/19/1999	
	A3	6,060,510		BRUSILOW	5/2000	
	A4	6,083,984		BRUSILOW	7/2000	
	A5	6,219,567		EGGERS	4/17/2001	
	A6	2004/0229948		SUMMAR	11/2004	
	A7	2006/0135612		FERRANTE	6/2006	
	A8	2008/0119554		JALAN	5/2008	
	A9	2010/0008859		SCHARSCHMIDT	1/14/2010	
	A10	2012/0022157		SCHARSCHMIDT		
	A11	2012/0220661		LEE	08/30/2012	
	A12	2013/0210914		SCHARSCHMIDT	08/15/2013	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent or Application Office	NUMBER	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	B1	WO	2005/053607		Medicis Pharmaceuticla Corp.	6/16/2005		
	B2	WO	2006/056794		UCL Business PCL	6/01/2006		
	B3	WO	2007/005633		Navinta LLC	01/11/2007		
	B4	WO	2009/087474		Akthelia Pharmaceuticals	7/16/2009		
	B5	WO	2009/134460		Hyperion Therapeutics	11/05/2009		
	B6	WO	2010/025303		Hyperion Therapeutics	03/04/2010		
	B7	WO	2012/028620		INSERM	03/08/2012		

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	C1	AMBROSE, A.M., (1933) "Further Studies on the Detoxification of Phyenylacetic Acid." *J Biol Chem* 101:669-675.	
	C2	BATSHAW M.L. et al. (1980, December) "Treatment of Hyperammonemic Coma Caused by Inborn Errors of Urea Synthesis," *J Pediatr* 97(6):893-900.	
	C3	BATSHAW M.L. et al. (1982, June 10) "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.	
	C4	BATSHAW, M.L. (1984) "Hyperammonemia," in Current Problems in Pediatrics, Lockhart, J.D. ed.: Year Book Medical Publishers, pp. 2-69.	
	C5	BATSHAW, M.L. et al. (1981, August) "New Approaches to the Diagnosis and Treatment of Inborn Errors of Urea Synthesis," *Pediatrics* 68(2):290-297.	
	C6	BERRY, G.T. et al., (2001) "Long-term Management of Patients with Urea Cycle Disorders." *J Pediatrics* 138:S56-S61.	
	C7	BRAHE, C., et al., (2005) "Phenylbutyrate Increases SMN Gene Expression in Spinal Muscular Atrophy Patients," *Eur J Hum Genet* 13:256-259.	
	C8	BRUNETTI-PIERRI, N., et al., (2011) "Phenylbutyrate Therapy for Maple Syrup Urine Disease," *Hum Mol Genet* 20(4):631-640.	
	C9	BRUSILOW, S.W., et al. (1979, September 1) "New Pathways of Nitrogen Excretion in Inborn Errors of Urea Synthesis," *Lancet* 2(8140):452- 454.	
	C10	BRUSILOW, S.W., et al. (1980, February 8) "Amino Acid Acylation: A Mechanism of Nitrogen Excretion in Inborn Errors of Urea Synthesis," *Science* 207:659-661.	
	C11	BRUSILOW, S.W., et al. (1984, June 21) "Treatment of Episodic Hyperammonemia in Children With Inborn Errors of Urea Synthesis," *N Engl J Med* 310(25):1630-1634.	
	C12	BRUSILOW, S.W., et al. (1991) "Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion. *Pediatric Res* 29(2):147-150.	
	C13	BRUSILOW, S.W., et al. (1991) "Treatment of Urea Cycle Disorders," Chapter 5 in Treatment of Genetic Diseases, Desnik, R.J. et al. eds, Churchill Livingstone, New York, New York, pp. 79-94.	

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	C14	BRUSILOW, S.W., et al. (1993) "Restoration of Nitrogen Homeostasis in a Man with Ornithine Transcarbamylase Deficiency." *J Metabolism* 42:1336-1339.	
	C15	BRUSILOW, S.W., et al. (1994, July 25 - 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.	
	C16	BRUSILOW, S.W., et al. (1995) "Urea Cycle Disorders: Clinical Paradigm of Hyperammonemic Encephalopathy." *Prog Liver Diseases* 12:293-309.	
	C17	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.	
	C18	BRUSILOW, S.W., et al. (1996) "Urea Cycle Disorders: Diagnosis, Pathophysiology, and Therapy," *Adv Pediatr* 43:127-170.	
	C19	CALLOWAY, D.H. et al. (1971) "Sweat and Miscellaneous Nitrogen Losses in Human Balance Studies," *J Nutrition* 101:775-786.	
	C20	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.	
	C21	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. October 20, 2006).	
	C22	CHANG, J. et al., (2001) "Treatment of Spinal Muscular Atrophy by Sodium Butyrate," *PNAS* 98(17):9808-9813.	
	C23	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.	
	C24	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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	C25	COMTE, B. et al., (2002) "Identification of Phenylbutyrylglutamine, A new Metabolite of Phenylbutyrate Metabolism in Humans," *J Mass Spectrometry*, 37(6):581-590.	
	C26	CUDKOWICZ, ALS (2009) "Phase 2 Study of Sodium Phenylbutyrate in ALS," *Amyotrophic Lateral Sclerosis* 10:99-106.	
	C27	DEFERRARI, G. et al. (1981) "Brain Metabolism of Amino Acids and Ammonia in Patients with Chronic Renal Insufficiency," *Kidney International* 20:505-510.	
	C28	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.	
	C29	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.	
	C30	ENNS, G.M., et al., (2007) "Survival After Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders," *N Eng J Med* 356:2282-2292.	
	C31	FDA Label for BUPHENYL, 6 pages.	
	C32	FDA. "Buphenyl® (Sodium Phenylbutyrate) Label" nine pages (August 2003).	
	C33	GARGOSKY, S. (August 2, 2005) "Improved Survival of Neonates Following Administration of Ammonul® (Sodium Phenyl acetate & Sodium Benzoate) 10% I 10% Injection," SSIEM Poster, six pages.	
	C34	GARGOSKY, S. et al. (October 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.	
	C35	GARGOSKY, S. (2006) "High Ammonia Levels Are Associated With Increased Mortality and Coma," Ucyclyd Pharma, Inc., one page.	
	C36	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.	

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	C37	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.	
	C38	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 (September-October 2008, e-pub. July 26, 2008).	
	C39	GROPMAN, A. (2010) "Brain Imaging in Urea Cycle Disorders," *Mol Genet Metab* 100:S20-S30.	
	C40	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.	
	C41	HOGARTH, P., et al., (2007) "Sodium Phenylbutyrate in Huntington's Disease: A Dose-Finding Study," *Mov Disord* 22(13):1962-1964.	
	C42	HUANG, H.H., et al., (2012) "Cannabinoid Receptor 2 Agonist Ameliorates Mesenteric Angiogenesis and Portosystemic Collaterals in Cirrhotic Rats," *Hepatology* 56:248-258.	
	C43	HYPERION THERAPEUTICS (2007, October 23) "Hyperion Therapeutics Announces Enrollment of First Patient in Phase 1/2 Clinical Trial of GT4P in Patients with Urea Cycle Disorders" Announcement, 1 page.	
	C44	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 April 27, 2011, three pages (March 30, 2009).	
	C45	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 April 27, 2011, three pages (June 2, 2009).	
	C46	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.	

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	C47	JOHN, B.A. et al. (2009, March) "The Disposition of HPN-100, A Novel Pharmaceutical Under Development for Potential Treatment of Hyperammonemia, in Cynomolgus Monkeys," ACMG 2009 ADME, poster, two pages.	
	C48	JOHN, B.A. et al. (2009, March) "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.	
	C49	KASUMOV, T. et al., (2004) "New Secondary Metabolites of Phenylbutyrate in Humans and Rats," *Drug Metabolism and Disposition* 32(1):10-19.	
	C50	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.	
	C51	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.	
	C52	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.	
	C53	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.	
	C54	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.	
	C55	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.	

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not criteria 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 application(s).

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				Group Art Unit	1765
				Examiner Name	
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OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume issue number(s), publisher, city and/or country where published.	T
	C56	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.	
	C57	LIANG, K.Y., et al., (1986) "Longitudinal Data Analysis Using Generalized Linear Models," *Biometrika* 73(1):13-22.	
	C58	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).	
	C59	MACARTHUR, R. B., et al., "Pharmacokinetics of sodium phenylacetate and soium benzoate following intravenous administrtion as both a bolus and continuous infusion to healthy adult volunteers." *Mol Genet Metab* 81:(1):S67-S73 (2004).	
	C60	MAESTRI, N.E. et al. "Plasma Glutamine Concentration: A Guide in the Management of Urea Cycle Disorders," *J Pediatr* 121(2):259-261(August 1992).	
	C61	MANSOUR, A. et al. "Abdominal Operations in Patients with Cirrhosis: Still A Major Surgical Challenge," *Surgery* 122(4):730-735. (Abstract Only.) (October 1997).	
	C62	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, April 28-May 1, 2008, two pages.	
	C63	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)	
	C64	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.	
	C65	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.	
	C66	MCGUIRE, B. et al., (2010) "Pharmacology and Safety of Glycerol Phenylbutyrate in Healthy Adults and Adults with Cirrhosis," *Hepatology* 51:2077-2085.	

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OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume issue number(s), publisher, city and/or country where published.	T
	C67	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.	
	C68	MERCURI, E., et al., (2004) "Pilot Trial of Phenylbutyrate in Spinal Muscular Atrophy," *Neuromuscul Disord* 14:130-135.	
	C69	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.	
	C70	MOLDAVE, K., et al., (1957) "Synthesis of Phenylacetylglutamine by Human Tissue," *J Biol Chem* 229:463-476.	
	C71	MONTELEONE, JPR, et al., (2012) “Population pk Analysis of Glycerol Phenylbutyrate (GPB) and Sodium Phenylbutyrate(NAPBA) in Adult and Pediatric Patients with Urea Cycle Discorders,” *Mol Genet Metab* 105:343.	
	C72	ONG, J. P., et al., (2003) "Correlation Between Ammonia Levels and the Severity of Hepatic Encephalopathy," *Am J Med* 114:188-193.	
	C73	PERRINE, S. P., (2008) "Fetal Globin Stimulant Therapies in the Beta-Hemoglobinopathies: Principles and Current Potential," *Pediatr Ann* 37(5):339-346.	
	C74	PISCITELLI, S.C. et al. (1995) "Disposition of Phenylbutyrate and its Metabolites, Phenylacetete and Phenylacetylglutamine," *J Clin Pharmacal* 35:368-373.	
	C75	PROPST, A. et al. (1995) "Prognosis and Life Expectancy in Chronic Liver Disease," *Dig Dis Sci* 40(8):1805-1815. (Abstract Only).	
	C76	RILEY, T.R. et al. (2001) "Preventive Strategies in Chronic Liver Disease: Part II. Cirrhoses," *Am Fam Physician* 64(10):1735-1740. (Abstract Only).	
	C77	RUDMAN, D., et al., (1973) "Maximal Rates of Excretion and Synthesis of Urea in Normal and Cirrhotic Subjects," *J Clin Invest* 52:2241-2249.	
	C78	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.	

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	C79	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.	
	C80	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.	
	C81	SINGH, (2001) "Consensus Statement from a Conference for the Management of Patients with Urea Cycle Disorders," *Suppl to J Pediatrics* 138(1):S1-S5.	
	C82	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.	
	C83	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.	
	C84	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 (October 2008, e-pub. July 17, 2008).	
	C85	SWEDISH ORPHAN INTERNATIONAL, "Urea Cycle Disorders an International Perspective," Poster, Symposium Swedish Orphan International, Barcelona, Spain, January 12, 2007, one page.	
	C86	TANNER, L. M., et al., (2007) "Nutrient intake in lysinuric protein intolerance." *J Inherited Metabolic Disease* 30(5):716-721.	
	C87	THIBAULT, A. et al., (1994) "A Phase I and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer," *Cancer Res* 54(7):1690-1694.	
	C88	THIBAULT, A., et al., (1995) "Phase I Study of Phenylacetate Administered Twice Daily to Patients with Cancer," *Cancer* 75(12):2932-2938.	
	C89	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. June 17, 2008).	

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	C90	WATERLOW, J.C. (1963) "The Partition of Nitrogen in the Urine of Malnourished Jamaican Infants," *Am J Clin Nutrition* 12:235-240.	
	C91	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.	
	C92	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.	
	C93	Combined Search and Examination Report for British Patent Application No. GB0915545.8, search completed October 8, 2009, report dated October 9, 2009.	
	C94	Combined Search and Examination Report for British Patent Application No. GB1013468.2, search completed September 8, 2010, report dated September 9, 2010.	
	C95	EUROPEAN PATENT OFFICE, Extended European Search Report for EP09739263 completed November 2, 2011.	
	C96	EUROPEAN PATENT OFFICE, International Search Report and Written Opinion for PCT/US2009/055256 completed December 18, 2009 and mailed December 30, 2009.	
	C97	Examination Report for British Patent Application No. GB0915545.8 dated February 5, 2010.	
	C98	Examination Report for British Patent Application No. GB0915545.8 dated May 11, 2010.	
	C99	Examination Report for British Patent Application No. GB0915545.8 dated October 27, 2010.	
	C100	Examination Report for British Patent Application No. GB1013468.2 dated October 28, 2011.	
	C101	International Preliminary Report on Patentability (Ch I) for PCT/US2012/028620, completed June 4, 2012 and mailed on April 10, 2014.	
	C102	International Preliminary Report on Patentability (Ch II) for PCT/US2012/028620, completed August 22, 2013 and mailed September 4, 2013.	

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	C103	International Preliminary Report on Patentability for PCT/US2009/030362, completed February 24, 2009 and mailed on March 10, 2011.	
	C104	International Preliminary Report on Patentability for PCT/US2009/055256, completed on August 27, 2009, mailed on March 10, 2011.	
	C105	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion for PCT/US2009/030362 mailed March 2, 2009.	
	C106	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion for PCT/US2012/028620 mailed June 20, 2012.	
	C107	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion for PCT/US2012/54673 mailed November 20, 2012.	
	C108	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion for PCT/US2013/71333 mailed March 28, 2014.	

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EFS ID:	20745483
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	34055
Filer:	Lara J. Dueppen/Deborah Muench
Filer Authorized By:	Lara J. Dueppen
Attorney Docket Number:	079532-8004.US01
Receipt Date:	19-NOV-2014
Filing Date:	11-SEP-2012
Time Stamp:	17:05:26
Application Type:	Utility under 35 USC 111(a)

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11	Non Patent Literature	Batshaw_M_1982_NEnglJMed_306_1387-92.PDF	985789 0f04db4a221e31ebcb01ec7a5700b2fe0a4d3252	no	6
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12	Non Patent Literature	Batshaw_M1984_CurrProblPediatr_2-69.PDF	3738234 e50ebed93b7a26ba3383935975f4e7bc0168e9e4	no	35
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Information:					
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Information:					
15	Non Patent Literature	Brahe_C_2005_EurJHumGenet_13_256-259.PDF	115135 8b0fab1febdd66cad229d931f42430338d393cb9	no	4
Warnings:					
Information:					
16	Non Patent Literature	Brunetti-Pierri_2011_HumMolGenet_20_631-640.PDF	262898 2b9223a07189ae82aedb9e49accea256a84692fc	no	10
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Information:					
17	Non Patent Literature	Brusilow_SW_1979_Lancet_2_452-454.PDF	664185 7366e8e3a38ada9b9be48ab8f707a9bb341f93cf	no	4
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Information:					
18	Non Patent Literature	Brusilow_SW_1980_Science_207_659-661.PDF	566788 a895af0c5f0417c1748284597b0c79c3565d09e7	no	3
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Warnings:					
Information:					
20	Non Patent Literature	Brusilow_SW_1991_ChurchillLivingstone_Ch5_79-94.PDF	925647 8f8919028954b9213afafbf2264a74d432db0c95	no	18
Warnings:					
Information:					
21	Non Patent Literature	Brusilow_SW_1993_JMetabolism_42_1336-1339.PDF	394026 1572d5d73bd837d8520dca6a790bd5a20ce7cc69	no	4
Warnings:					
Information:					
22	Non Patent Literature	Brusilow_SW_1995_ProgLivDis_12_293-309.PDF	766755 29e49a8537ed78b61512d5661b0a912f6c5be39d	no	17
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23	Non Patent Literature	Brusilow_SW_1995_MetMolBasesInherDis_1187-1232.PDF	2259764 29892c95c3df02f1ed1b78a61edb4019b2a40f14	no	48
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Warnings:					
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Warnings:					
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26	Non Patent Literature	Calloway_D_1971_JNutrition_101_205-216.PDF	1644481 dea403dcc6757379313f5b32aeb53837e61626c9	no	12
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Information:					
27	Non Patent Literature	Camacho_L_2007_InvestNewDrugs_25_131-138.PDF	299331 30e854ca3e83b36e1910e960e30f49f5b907ed93	no	8
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Information:					
28	Non Patent Literature	Chang_J_PNAS_2001_98_9808-9813.PDF	730431 ce6cd92a92687c6b9cbf74675a3533ffffd41569	no	6

Warnings:					
Information:					
29	Non Patent Literature	Chung_YL_ClinCancerRes_2000_6_1452-1458.PDF	750618 2ff26b5a3a6db9969211cd8c2f43dd2e14910501	no	8
Warnings:					
Information:					
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Warnings:					
Information:					
31	Non Patent Literature	Comte_B_2002_JMassSpectrometry_37_581-590.PDF	683712 4aacf9f4ff1743204bd225424f98f5dccf76f5c5	no	10
Warnings:					
Information:					
32	Non Patent Literature	Cudkowicz_M_2009_AmyotrophicLateralSclerosis_10_99-1106.PDF	123014 c38180d9a9bd4706d6ca6dce4c617a9021961a49	no	8
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Information:					
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34	Non Patent Literature	Diaz_GA_2011_MolGenetMetab_102_276.PDF	168683 21d1de3dcae3b6a51cf84586bc0e7b79ab521bdc	no	1
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35	Non Patent Literature	Enns_GM_2007_NEngJMed_356_2282-2292.PDF	222044 8c38e91725e2fb538cc51886287f207545f9b762	no	11
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Warnings:					
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Warnings:					
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38	Non Patent Literature	Gropman_A_2008_MolGenetMetab_95_21-30.PDF	1349320 ad58901fe3bb63afb3bf59d284f59ecbf5e3232d	no	10
Warnings:					
Information:					
39	Non Patent Literature	Gropman_A_2010_MolGenetMetab_100_S20-S30.PDF	1566360 f2ef8b75ca076e6672115c6db4239569c794dc86	no	11
Warnings:					
Information:					
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Warnings:					
Information:					
41	Non Patent Literature	Hogarth_P_2007_MovDisorders_22_1962-1964.PDF	57861 7c1d94ea74bd8ac5dad1ac1de21d3be6fc801908	no	3
Warnings:					
Information:					
42	Non Patent Literature	Huang_H_2012_Hepatology_56_248-258.PDF	1455550 ffe291036302ede5513c387082ac265daa701689	no	11
Warnings:					
Information:					
43	Non Patent Literature	HyperionPressRes_10232007.PDF	87009 4ebd52e262a117abe39c5b2bc90109b59740be2d	no	1
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44	Non Patent Literature	HyperionPressRes_03302009.PDF	187356 7a2889a74ab5eeef376a18d1587554a549d4163c	no	3
Warnings:					
Information:					
45	Non Patent Literature	HyperionPressRes_06022009.PDF	206909 cb6a7cc26ae4bac59a6fb3536cc50d08a80fa5c9	no	3
Warnings:					
Information:					
46	Non Patent Literature	James_MO_1972_ProcRSocLond_182_25-25.PDF	1188944 45fa8296c4a5068c81f082772d0ab950c3a43ddc	no	11

Warnings:					
Information:					
47	Non Patent Literature	John_BA_ACMG_2009_ADME_Abstract.PDF	54507 af12217c09f108ef736e0193b2986d523c8c8c60	no	1
Warnings:					
Information:					
48	Non Patent Literature	Kasumov_T_2004_DrugMetabDisp_32_10-19.PDF	1167314 7ee7cefb36b54ad2745e955d678bca216b20bba0	no	10
Warnings:					
Information:					
49	Non Patent Literature	Lee_B_2008_JInheritMetabolDis_31_91_362-P.PDF	121649 da88cf35faaec62aa50b083cfedaed9190182495	no	1
Warnings:					
Information:					
50	Non Patent Literature	Lee_B_2009_ICIEM_Poster.PDF	265527 53d5a8909673dc73e4efa8bde3d01d92e5acf455	no	1
Warnings:					
Information:					
51	Non Patent Literature	Lee_B_2009_ACMG_UCD_phase_II_abstract_FINAL.PDF	44330 c57838f3af084511732ead17e5512c037b1668a5	no	1
Warnings:					
Information:					
52	Non Patent Literature	Lee_B_2009_ACMG_17pgs.PDF	991128 b0eb092c5a1742655a7f682a361290903c4c4add	no	17
Warnings:					
Information:					
53	Non Patent Literature	Lee_B_2010_MolGenetMetab_100_221-228.PDF	750661 a68aca842a29e4c2ab318dcdb0df43024560acd6	no	9
Warnings:					
Information:					
54	Non Patent Literature	Liang_K-Y_1986_Biometrika_73_13-22.PDF	588858 fca9e1c6564162ecc877106021b95c5f8e065d70	no	10
Warnings:					
Information:					
55	Non Patent Literature	Lichter-Konecki_2011_MolGenetMetab_103_323-329.PDF	705287 95395548b41e64b01837ff15f8bfb5a15e0d7bee	no	7

Warnings:					
Information:					
56	Non Patent Literature	MacArthur_R_2004_MolGenetMetab_81_S67-S73.PDF	561963 746a835e6027bdc8736af5b80d226dbb8662c7e6	no	7
Warnings:					
Information:					
57	Non Patent Literature	Maestri_N_1992_JPediatr_121_259-261.PDF	126144 ea0ee41d1f3a1418566543be32e48848e8344550	no	3
Warnings:					
Information:					
58	Non Patent Literature	McGuire_B_2008_LiverInternational_28_743.PDF	61061 8f4d9eb4c227893220fae79d10a455389334eaef	no	1
Warnings:					
Information:					
59	Non Patent Literature	McGuire_B_2009_DDW_Poster.PDF	262060 26f9ff8c526e42dedfeeaee37dc1eeada5728b65	no	1
Warnings:					
Information:					
60	Non Patent Literature	McGuire_B_2010_Hepatology_51_2077-2085.PDF	815101 eeff9a09c15197cca51da025eefc8c91c5d33f25	no	9
Warnings:					
Information:					
		Total Files Size (in bytes):	58503613		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: BRUCE SCHARSCHMIDT ET AL.	CONF. NO: 1957
APPLICATION NO.: 13/610,580	ART UNIT: 1765
FILED: SEPTEMBER 11, 2012	
FOR: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS	

Information Disclosure Statement Within Three Months of Application Filing or Before First Action – 37 C.F.R. § 1.97(b)

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

Sir:

1. Timing of Submission

This information disclosure is being filed within three months of the filing date of this application or date of entry into the national stage of an international application or before the mailing date of a first Office action on the merits, whichever occurs last [37 C.F.R. § 1.97(b)]. The references listed on the enclosed Form PTO-1449 (modified) may be material to the examination of this application; the Examiner is requested to make them of record in the application.

2. Cited Information

☒ Copies of the following references are enclosed:

- ☒ All cited references
- ☐ References marked by asterisks
- ☐ The following:

☐ Copies of the following references can be found in parent U.S. Application No. <>:

- ☐ All cited references
- ☐ All references
- ☐ The following:

☒ This application was filed after 30 June 2003 and no copies of U.S. patents nor published applications are enclosed (See Notice of Deputy Commissioner Kunin on 11 July 2003).

☐ The following references are not in English. For each such reference, the undersigned has enclosed (i) a translation of the reference; (ii) a copy of a communication from a foreign patent office or International Searching Authority citing the reference, (iii) a copy of a reference which appears to be an English-language counterpart, or (iv) an English-language abstract for the reference prepared by a third party. Applicant has not verified that the translation, English-language counterpart or third-party abstract is an accurate representation of the teachings of the non-English reference, though, and reserves the right to demonstrate otherwise.

- ☐ All cited references
- ☐ References marked by ampersands
- ☐ The following:

3. Effect of Information Disclosure Statement (37 C.F.R. § 1.97(h))

This Information Disclosure Statement is not to be construed as a representation that: (i) a search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the cited information is, or is considered to be, material to patentability. In addition, applicant does not admit that any enclosed item of information constitutes prior art to the subject invention and specifically reserves the right to demonstrate that any such reference is not prior art.

4. Fee Payment

No fees are believed due because this Information Disclosure Statement is being filed before the mailing date of the first Office Action.

☐ Applicant further submits that no fee is due in light of the following certification under 37 C.F.R. § 1.97(e) (check only one):

- ☐ In accordance with 37 C.F.R. § 1.97(e)(1), the undersigned hereby states that each item of information submitted herewith was cited in a communication from a foreign patent office in a counterpart

foreign application not more than three months prior to the filing of this statement; or

☐ In accordance with 37 C.F.R. § 1.97(e)(2), the undersigned hereby states that no item of information submitted herewith was cited in a communication from a foreign patent office in a counterpart foreign application, or, to the knowledge of the person signing the certification after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c), more than three months prior to the filing of this statement.

However, should the Commissioner determine that fees are due in order for this Information Disclosure Statement to be considered, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-2586.

5. Patent Term Adjustment (37 C.F.R. § 1.704(d))

☐ The undersigned states that each item of information submitted herewith was cited in a communication from a foreign patent office in a counterpart application and that this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty days prior to the filing of this statement. 37 C.F.R. § 1.704(d).

Respectfully submitted,
Perkins Coie LLP

Date: November 19, 2014

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/610,580	09/11/2012	Bruce Scharschmidt	079532-8004.US01	1957

34055 7590 02/27/2015

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

EXAMINER
TOWNSLEY, SARA ELIZABETH

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
02/27/2015	ELECTRONIC

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

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

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

patentprocurement@perkinscoie.com

Office Action Summary	Application No. 13/610,580	Applicant(s) SCHARSCHMIDT ET AL.	
	Examiner SARA E. TOWNSLEY	Art Unit 1629	AIA (First Inventor to File) Status No

-- 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* MONTHS 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 *11/4/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1,2,5-7 and 9-13* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,2,5-7 and 9-13* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

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

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *11/19/2014*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

NON-FINAL REJECTION

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

This application, filed Sep. 11, 2012, claims benefit of priority to provisional application 61/636,256, filed Apr. 20, 2012.

Claims 1, 2, 5-7, and 9-13, as amended, are pending.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Election/Restrictions

Applicant's election without traverse of the compound species HPN-100 (glycerol phenylbutyrate, CAS Registry No. 611168-24-2), and urea cycle disorder as the species of medical condition treated, in the reply filed on Nov. 4, 2014 is acknowledged.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on Nov. 19, 2014 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Objections

1. Claims 1, 2, 5-7, and 9-13 are objected to because of the following informalities: the first recitation of "PAA" should spell out in full the term for which it is an abbreviation, phenylacetic acid. Similarly, the first recitation of "PAGN" should spell out in full the term for which it is an abbreviation, phenylacetyl glutamine.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

2. The following is a quotation of pre-AIA 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.

3. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1, 2, 5-7, and 9-13 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Scharschmidt (US Pub. 2012/0022157) in view of McGuire et al.

(*Hepatology* 51, 2077-2085 (2010)) (cited as references A9 and C66, respectively, on the IDS dated Nov. 19, 2014).

Independent claim 1 recites a method of treating a nitrogen retention disorder in a subject; and **independent claim 5** recites a method of adjusting the dosage of a PAA prodrug, each comprising the steps of

(a) administering a first dosage of a PAA prodrug,

(b) measuring plasma PAA and PAGN levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range,

where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased, and

a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the PAA prodrug based on the determination in (d).

Scharschmidt discloses a method of treating a nitrogen retention disorder in a subject (para [0173]) comprising:

(a) administering a first dosage of a PAA prodrug (para [0173]) and

(b) measuring urinary PAGN levels (para [0174]).

However, Scharschmidt does not disclose measuring PAA or PAGN levels in plasma, or (c) calculating a plasma PAA:PAGN ratio.

Scharschmidt further teaches the step of determining whether the PAA prodrug dosage needs to be adjusted based on whether the measured levels of PAGN falls within a target range (para [0174], [0106]).

However, Scharschmidt does not teach wherein the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased.

Scharschmidt also discloses the step of (e) administering a second dosage of the PAA prodrug based on the determination in (d) (para [0106], [0174]).

McGuire discloses measuring metabolites in blood and urine after administration of a PAA prodrug (abstract), wherein the metabolites include plasma PAA and PAGN (page 2079, col 2, para 3), and comparing these values as a ratio (pg 2081, col 1, para 2). McGuire further teaches that urinary testing is not as complete and thorough as plasma testing (pg 2081, col 2, para 1), and that metabolites important in the monitoring of PAA prodrugs include both PAA and PAGN.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Scharschmidt by measuring plasma levels of PAA and PAGN, instead of urinary PAA and PAGN, and comparing them as a ratio, in order to more accurately assess the patient's metabolism of PAA prodrugs, and evaluate any need to adjust the dosage, with a reasonable expectation of success, because McGuire teaches that urinary testing is not as complete and thorough as testing for plasma levels of PAA and PAGN.

Independent claim 2 recites a method of treating a nitrogen retention disorder in a subject who has previously been administered a first dosage of a PAA prodrug; and **independent claim 6** recites a method of optimizing the therapeutic efficacy of a PAA prodrug in a subject who has previously been administered a first dosage of a PAA prodrug, each comprising the steps of

(a) measuring plasma PAA and PAGN levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the first PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(d) administering a second dosage of the PAA prodrug based on the determination in (c).

Scharschmidt teaches a method of treating a nitrogen retention disorder in a subject who has previously been administered a first dosage of a PAA prodrug (para [0106], [0173]) comprising measuring PAGN levels (para [0174]). Scharschmidt also teaches a method of optimizing the therapeutic efficacy of a PAA prodrug in a subject (para [0297],[0173]) who has previously been administered a first dosage of a PAA prodrug (para [0106]) comprising measuring PAGN levels (para [0174]).

However, Scharschmidt does not disclose measuring PAA or PAGN levels in plasma, or (c) calculating a plasma PAA:PAGN ratio.

Scharschmidt further teaches the step of determining whether the PAA prodrug dosage needs to be adjusted based on whether the measured levels of PAGN falls within a target range (para [0174], [0106]).

However, Scharschmidt does not teach wherein the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased.

Scharschmidt also discloses the step of (d) administering a second dosage of the PAA prodrug based on the determination in (c) (para [0106], [0174]).

McGuire discloses measuring metabolites in blood and urine after administration of a PAA prodrug (abstract), wherein the metabolites include plasma PAA and PAGN (page 2079, col 2, para 3), and comparing these values as a ratio (pg 2081, col 1, para 2). McGuire further teaches that urinary testing is not as complete and thorough as plasma testing (pg 2081, col 2, para 1), and that metabolites important in the monitoring of PAA prodrugs include both PAA and PAGN.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Scharschmidt by measuring plasma levels of PAA and PAGN, instead of urinary PAA and PAGN, and comparing them as a ratio, in order to more accurately assess the patient's metabolism of PAA prodrugs, and evaluate any need to adjust (optimize) the dosage, with a reasonable expectation of success, because McGuire teaches that urinary testing is not as complete and thorough as testing for plasma levels of PAA and PAGN.

Scharschmidt discloses that in some embodiments, the nitrogen retention disorder is the elected condition, a UCD (urea cycle disorder), as recited by claim 7; and that the PAA prodrug can be the elected compound, HPN-100 (para. [0097]), as recited by claim 13.

While Scharschmidt does not disclose that the PAA:PAGN ratio falls within a target range of 1 to 2.5, as recited by claim 9, or within a target range of 1 to 2, as recited by claim 10, it would have been *prima facie* obvious to an ordinarily skilled clinician to determine the optimal target range for the plasma PAA:PAGN ratio for the subject being treated, by routine experimentation.

Scharschmidt further teaches measurement PAGN levels is carried out after the first dosage of PAA prodrug has had sufficient time to reach steady state (para [0160]), but does not disclose measurement of PAA levels, as recited by claim 11. However, it would have been *prima facie* obvious to an ordinarily skilled clinician to further measure PAA as well as PAGN in order to maintain comparable results, by routine experimentation.

Scharschmidt further teaches measurement of PAGN levels 48 hours to 1 week after the first dosage of PAA prodrug is administered (para (0160), 3 days), but does not disclose measurement of PAA levels, as recited by claim 12. However, it would have been *prima facie* obvious to an ordinarily skilled clinician to further measure PAA as well as PAGN in order to maintain comparable results, by routine experimentation.

The rationale to combine and modify Scharschmidt and McGuire is premised on the findings that (1) the prior art includes each element claimed, with the only difference

between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference; (2) one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately; and (3) one of ordinary skill in the art would have recognized that the results of the combination were predictable.

As recognized by MPEP §2143, combining prior art elements according to known methods to yield predictable results would motivate the skilled artisan to modify the references with a reasonable expectation of success. The rationale to support a conclusion of *prima facie* obviousness is that all the claimed elements were known in the prior art, and a skilled artisan could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. See *KSR Int'l Co. v. Teleflex Inc.* (550 U.S. 398, 409).

Double Patenting

5. 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 double patenting rejection is appropriate where the claims at issue 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 reference 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. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

6. Claims 1, 2, 5-7, and 9-13 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3, 6, 8, 11, and 12 of **U.S. Patent No. 8,642,012** in view of McGuire et al. (*Hepatology* 51, 2077-2085 (2010), cited above).

Reference claims 1, 3, and 6 are drawn to methods of treating a patient having a urea cycle disorder comprising

(a) determining a target urinary phenylacetyl glutamine (PAGN) output

(b) calculating an effective initial dosage of a phenylacetic acid (PAA) prodrug, e.g., HPN-100, wherein the effective dosage of PAA prodrug is calculated based on a mean conversion of PAA prodrug to urinary PAGN of about 60%; and

(c) administering the effective initial dosage of PAA prodrug to the patient;

wherein administration of the effective initial dosage of PAA prodrug produces a normal plasma ammonia level in the patient.

Reference claims 8, 11, and 12 are drawn to methods of administering a phenylacetic acid (PAA) prodrug, e.g., HPN-100, to a patient having a urea cycle disorder comprising

(a) administering a first dosage of the PAA prodrug;

(b) determining urinary phenylacetyl glutamine (PAGN) excretion following administration of the first dosage of the PAA prodrug;

(c) determining an effective dosage of the PAA prodrug based on the urinary PAGN excretion, wherein the effective dosage is based on a mean conversion of PAA prodrug to urinary PAGN of about 60%; and

(d) administering the effective dosage to the patient,

wherein administration of the effective dosage of PAA prodrug produces a normal plasma ammonia level in the patient.

McGuire discloses measuring metabolites in blood and urine after administration of a PAA prodrug (abstract), wherein the metabolites include plasma PAA and PAGN (page 2079, col 2, para 3), and comparing these values as a ratio (pg 2081, col 1, para 2). McGuire further teaches that urinary testing is not as complete and thorough as plasma testing (pg 2081, col 2, para 1), and that metabolites important in the monitoring of PAA prodrugs include both PAA and PAGN.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of the reference claims by measuring plasma levels of PAA and PAGN, instead of urinary PAA and PAGN, and comparing them as a ratio, in order to more accurately assess the patient's metabolism of PAA prodrugs, and evaluate any need to adjust (optimize) the dosage, with a reasonable expectation of success, because McGuire teaches that urinary testing is not as complete and thorough as testing for plasma levels of PAA and PAGN. In addition, it

would have been *prima facie* obvious to an ordinarily skilled clinician to further measure PAA as well as PAGN, and to determine the optimal target range for the plasma PAA:PAGN ratio by routine experimentation.

Conclusion

Claims 1, 2, 5-7, and 9-13 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. TOWNSLEY whose telephone number is 571-270-7672. The examiner can normally be reached on Mon-Fri from 9:00 am to 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff S. Lundgren, can be reached at 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SARA E. TOWNSLEY/
Examiner, Art Unit 1629

UNITED STATES PATENT AND TRADEMARK OFFICE

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

BIB DATA SHEET

CONFIRMATION NO. 1957

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/610,580	09/11/2012	514	1629	079532-8004.US01

APPLICANTS

INVENTORS

Bruce Scharschmidt, San Francisco, CA;
Masoud Mokhtarani, Walnut Creek, CA;

**** CONTINUING DATA ***************************

This appln claims benefit of 61/636,256 04/20/2012

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
09/24/2012

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /SARA ELIZABETH TOWNSLEY/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	7	10	4

ADDRESS

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

TITLE

METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

FILING FEE RECEIVED		
1139	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

BIB (Rev. 05/07).

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13610580	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SARA E TOWNSLEY	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/05/2014	02/20/2015							
	1	÷	✓							
	2	÷	✓							
	3	-	-							
	4	-	-							
	5	÷	✓							
	6	÷	✓							
	7	÷	✓							
	8	-	-							
	9	÷	✓							
	10	÷	✓							
	11	÷	✓							
	12	÷	✓							
	13	÷	✓							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13610580	SCHARSCHMIDT ET AL.
	Examiner	Art Unit
	SARA E TOWNSLEY	1629

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
61/636,256 considered	2/20/2015	set
Inventor name/assignee search (PALM, EAST)	2/20/2015	set
EAST keyword search (USPAT, PGPub, USOCR, EPO, JPO, Derwent)	2/20/2015	set

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/SARA E TOWNSLEY/ Examiner, Art Unit 1629	

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	7	"8404215".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2015/02/23 10:20
L6	674	scharschmidt.in. or mokhtarani.in. or hyperion.as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2015/02/23 10:22
L7	539	urea cycle disorder	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2015/02/23 10:22
L8	14	L6 and L7	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2015/02/23 10:22
L9	20	L6 and plasma.clm.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2015/02/23 10:22
S1	2	"20130281530".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 12:37
S2	2	"5968979".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 12:38
S3	2	WO "2009134460"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:05
S4	2	"8642012".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:06
S5	2	"20100008859".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:07
S6	666	scharschmidt.in. or mokhtarani.in. or hyperion.as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:10
S7	72	HPN-100 or HPN100 or HPN "100"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:10
S8	14	S6 and S7	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:10
S9	517	urea cycle disorder	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:11
S10	13	S7 and S9	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:12
S11	29	brusilow.in.	US-PGPUB; USPAT; USOCR; EPO; JPO;	ADJ	ON	2014/11/26 13:13

			DERWENT			
S12	3	PAA WITH PAGN WITH ratio	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:13
S13	3	"4284647".pn.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:34
S14	77	HPN-100 or HPN100 or HPN "100" or glycerol phenylbutyrate	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2014/11/26 13:39

EAST Search History (Interference)

<This search history is empty>

2/23/2015 10:25:32 AM
C:\Users\stownsley\Documents\EAST\Workspaces\13610580.wsp

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

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

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

I hereby appoint:

■ Practitioners associated with Customer Number: 101325

OR

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

Name	Registration Number	Name	Registration Number

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

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

■ The address associated with Customer Number: 101325

OR

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

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

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

SIGNATURE of Assignee of Record

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

Signature	[signature]	Date	5/11/15
Name	Brian K. Beeler	Telephone	847-502-5250
Title	Senior VP, Legal		

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

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: HORIZON THERAPEUTICS, INC.

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

Titled:

HORIZON THERAPEUTICS, INC., a Delaware Corporation

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

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

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

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

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

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

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

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

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

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

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

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

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

   1. From: _____ To: _____

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

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

   2. From: _____ To: _____

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

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

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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

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

4. From: _____ To: _____

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

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

5. From: _____ To: _____

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

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

6. From: _____ To: _____

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

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

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

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

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

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

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

[Page 2 of 2]

Schedule A

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

Electronic Acknowledgement Receipt

EFS ID:	22364015
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	34055
Filer:	Dennis A. Bennett/Ronnie Almira
Filer Authorized By:	Dennis A. Bennett
Attorney Docket Number:	079532-8004.US01
Receipt Date:	15-MAY-2015
Filing Date:	11-SEP-2012
Time Stamp:	17:06:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

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

Warnings:	
Information:	

2	Assignee showing of ownership per 37 CFR 3.73	HOR_373-Statment_Schedule_A.pdf	157428 6c05c96d65f079637c44f6e854cbea479726c476	no	3

Warnings:	
Information:	
Total Files Size (in bytes):	253934

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/610,580	09/11/2012	Bruce Scharschmidt	079532-8004.US01

CONFIRMATION NO. 1957

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

POA ACCEPTANCE LETTER

OC000000075260399

Date Mailed: 05/20/2015

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

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

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

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

/ytdemisse/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/610,580	09/11/2012	Bruce Scharschmidt	079532-8004.US01

CONFIRMATION NO. 1957

POWER OF ATTORNEY NOTICE

34055
PERKINS COIE LLP - LOS General
POST OFFICE BOX 1247
SEATTLE, WA 98111-1247

OC000000075259839

Date Mailed: 05/20/2015

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

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

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

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

/ytdemisse/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Scharschmidt et al. Confirmation No. 1957

Application No.: 13/610,580 Examiner: Sara Elizabeth Townsley

Filing Date: September 11, 2012 Group Art Unit: 1629

For: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

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

AMENDMENT

Sir:

This Amendment is responsive to the Non-Final Official Action mailed February 27, 2015 regarding the above-referenced patent application. Please amend the above-identified application as shown and reconsider the rejections of the claims for at least the reasons presented in the following remarks.

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

Remarks follow the Amendments to the Claims.

Amendments to the Claims:

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

1. (Currently Amended) A method of treating urea cycle disorders ~~a nitrogen retention disorder~~ in a subject comprising:

(a) administering a first dosage of glyceryl tri-[4-phenylbutyrate] ~~a PAA prodrug~~,

(b) measuring plasma phenylacetic acid (PAA) [[PAA]] and phenylacetyl glutamine (PAGN) [[PAGN]] levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the glyceryl tri-[4-phenylbutyrate] ~~PAA prodrug~~ dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] ~~PAA prodrug~~ based on the determination in (d).

2. (Currently Amended) A method of treating urea cycle disorders ~~a nitrogen retention disorder~~ in a subject who has previously been administered a first dosage of glyceryl tri-[4-phenylbutyrate] ~~a PAA prodrug~~ comprising:

(a) measuring plasma phenylacetic acid (PAA) [[PAA]] and phenylacetyl glutamine (PAGN) [[PAGN]] levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the first ~~PAA prodrug~~ dosage of glyceryl tri-[4-phenylbutyrate] needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(d) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] ~~PAA prodrug~~

based on the determination in (c).

3. (Cancelled)

4. (Cancelled)

5. (Currently Amended) A method of adjusting the dosage of glyceryl tri-[4-phenylbutyrate] ~~a PAA prodrug~~ comprising:

(a) administering a first dosage of glyceryl tri-[4-phenylbutyrate] ~~a PAA prodrug~~,

(b) measuring plasma phenylacetic acid (PAA) [[PAA]] and phenylacetyl glutamine (PAGN) [[PAGN]] PAGN levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the glyceryl tri-[4-phenylbutyrate] ~~PAA prodrug~~ dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] ~~PAA prodrug~~ based on the determination in (d).

6. (Currently Amended) A method of optimizing the therapeutic efficacy of glyceryl tri-[4-phenylbutyrate] ~~a PAA prodrug~~ in a subject who has previously been administered a first dosage of glyceryl tri-[4-phenylbutyrate] ~~a PAA prodrug~~ comprising:

(a) measuring plasma phenylacetic acid (PAA) [[PAA]] and phenylacetyl glutamine (PAGN) [[PAGN]] PAGN levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the ~~PAA prodrug~~ dosage of glyceryl tri-[4-phenylbutyrate] needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] ~~PAA prodrug~~ as necessary based on the determination in (c).

7. (Cancelled)

8. (Cancelled)

9. (Previously Presented) The method of any of claims 1, 2, 5, or 6, wherein the target range is 1 to 2.5.

10. (Previously Presented) The method of any of claims 1, 2, 5, or 6, wherein the target range is 1 to 2.

11. (Currently Amended) The method of any of claims 1, 2, 5, or 6, wherein measurement of PAA and PAGN levels is carried out after the first dosage of glyceryl tri-[4-phenylbutyrate] ~~PAA prodrug~~ has had sufficient time to reach steady state.

12. (Currently Amended) The method of claim 11, wherein measurement of PAA and PAGN levels is carried out 48 hours to 1 week after the first dosage of glyceryl tri-[4-phenylbutyrate] ~~PAA prodrug~~ is administered.

13. (Cancelled)

REMARKS

Claims 7 and 13 have been cancelled with prejudice or disclaimer. Claims 1, 2, 5, 6, 11, and 12 have been amended. No new matter has been added by these amendments. Upon entry of this amendment, claims 1, 2, 5, 6, and 9-12 are pending.

Claim Objections

The Office has objected to the claims because of certain informalities. Specifically, the Office requests that the first recitations of "PAA" and "PAGN" should spell out in full the respective terms for which they stand. Applicant has amended the claims accordingly. Applicant requests that the objections be withdrawn.

Rejections under 35 U.S.C. § 103(a) (pre-AIA)

Claims 1, 2, 5-7, and 9-13 have been rejected under 35 U.S.C. § 103(a), as allegedly obvious over US Pub 2012/0022157 ("Scharschmidt") in view of McGuire et al. Hepatology 51, 2077-2085 (2010) ("McGuire"). The Office alleges that Scharschmidt discloses at [0173] a method of treating a nitrogen disorder in a subject, comprising (a) administering a PAA prodrug ([0173]), and (b) measuring urinary PAGN levels ([0174]). The Office acknowledges that Scharschmidt does not teach measuring the PAA and PAGN levels in plasma, or calculating the PAA/PAGN ratio. The Office also acknowledges that Scharschmidt does not teach using the PAA/PGN ratio in comparison to a target range to determine whether the PAA prodrug dosage needs to be decreased or increased. The Office alleges that the teachings in McGuire regarding measuring metabolites, including PAA and PAGN, of PAA prodrugs in plasma, and comparing these values as a ratio, together with the teachings of Scharschmidt, would lead the person of ordinary skill in the art at the time the present invention was made to measure plasma levels of PAA and PAGN in a patient taking a PAA prodrug, and use the PAA/PAGN ratio to adjust the dosage of the PAA prodrug. Applicant respectfully disagrees.

McGuire describes a statistical approach to assess bioequivalency of 2 different drugs (glycerol phenylbutyrate [GPB] as compared with sodium phenylbutyrate [NaPBA]). The ratio referred to by McGuire is a ratio of the geometric means of the systemic exposure to the same individual metabolites (PBA, PAA or PAGN) during dosing with GPB as compared NaPBA that is calculated as follows:

$$\text{Ratio} = \frac{\text{(PBA blood levels on GPB)}}{\text{(PBA blood levels on NaPBA)}}$$

wherein the systemic exposure is calculated based on PBA levels taken at multiple time points from multiple patients during dosing with each of the two different drugs (multiple samples from multiple patients on two different drugs). McGuire simply utilizes the conventional methodology for assessing bioequivalence of one drug to another, which involves comparing the ratio of the systemic exposure to the same metabolite, in this case PBA, during dosing with GPB as compared with NaPBA wherein the comparison of the two is expressed as a ratio. The same approach would be used for the other metabolites, including PAA and PAGN. Calculating the ratio of geometric means is a well-established statistical approach that is accepted by the field and regulatory authorities for assessing bioequivalence of 2 different drugs.

Importantly, McGuire does not teach the novel and unexpected finding that the ratio of two *different* metabolites; i.e,. PAA and PAGN, taken at the *same* time from the *same* patient receiving either glyceryl tri-[4-phenylbutyrate] (GPB) is of utility in assessing the effectiveness of PAA to PAGN conversion and, therefore, useful in identifying patients who are likely to experience high levels of PAA, a potentially toxic metabolite, and in whom dose reduction may be needed. The present invention teaches use of the following formula:

$$\text{Ratio} = \frac{\text{(PAA blood level on GPB)}}{\text{(PAGN blood level on GPB)}}$$

wherein the ratio represents the plasma level of PAA divided by the plasma level of PAGN and where both blood samples are taken from the same patient at exactly the same time (one sample from one patient on one drug).

Applicants have discovered that measuring the PAA/PAGN ratio provides an unexpectedly accurate measure of PAA prodrug metabolism in subjects with nitrogen retention disorders and/or hepatic impairment. This is important because high levels of PAA in circulation cause reversible toxicity (see specification at paragraph [0010]), and conversion of PAA to PAGN is a saturable process that varies considerably among individuals (specification at paragraph [0028]. Because PAA, PAGN, and ammonia levels do not provide information on whether a subject is effectively converting a PAA prodrug to PAGN, before the present invention was made there was lacking a

method to evaluate conversion of a PAA prodrug to PAGN on an individual basis, to provide improved methods of adjusting PAA prodrug dosage.

McGuire teaches the comparison of the same metabolite in patients taking different drugs, for the purpose of assessing bioequivalence of two different drugs. Nothing in McGuire teaches or suggests measuring two different metabolites from glyceryl tri-[4-phenylbutyrate] in the same patient, and using the ratio of the two metabolites from the same patient to adjust the dosage of the glyceryl tri-[4-phenylbutyrate]. Because the element of measuring plasma levels of PAA and PAGN in a single patient following treatment with glyceryl tri-[4-phenylbutyrate], and calculating the PAA/PGN ratio and comparing to a target range, is not taught or suggested by McGuire, the combination of references cited by the Office fails to teach all elements of the claimed invention. For at least these reasons, Applicant respectfully requests that the rejection be withdrawn.

Double Patenting

The claims have been rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3, 6, 8, 11, and 12 of U.S. Patent No. 8,642,012 in view of McGuire. Solely to expedite prosecution and without in any way conceding to the rejection, Applicant submits a terminal disclaimer herewith. Applicant requests that the rejection be withdrawn.

The Examiner is invited to contact the undersigned by telephone or email if it is felt that an interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees due and any other fees under 37 C.F.R. § 1.16 or § 1.17 during the pendency of this application to our Deposit Account No. 50-4297.

Respectfully submitted,

/Lauren L. STEVENS/

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Attorney for Applicants
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Scharschmidt et al. Confirmation No. 1957

Application No.: 13/610,580 Examiner: Sara Elizabeth Townsley

Filing Date: September 11, 2012 Group Art Unit: 1629

For: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

NOTICE OF RELATED LITIGATION

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

Applicant hereby notifies the U.S. Patent and Trademark Office that the subject matter of the present application is involved in litigation in the United States.

Specifically, Par Pharmaceutical, Inc. ("Par") sent a PIV notice letter to Hyperion Therapeutics, Inc. ("Hyperion") on March 12, 2014 providing notice that Par had filed an Abbreviated New Drug Application ("ANDA") with respect to RAVICTI® (Glycerol Phenylbutyrate) Oral Liquid, with a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") alleging that U.S. Patent Nos. 8,404,215 and 8,642,012 are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the Watson drug product.

Under 21 U.S.C. § 355(j)(5)(B)(iii), Hyperion had forty-five days from receipt of the ANDA notice letter to file suit against Watson for patent infringement. Accordingly, on April 23, 2014, Hyperion brought suit on those patents against Par in the United States District Court for the Eastern District of Texas, Marshall Division. The Complaint alleged that Par infringes U.S. Patent Nos. 8,404,215 and 8,642,012. Subsequently, in May of 2015, Horizon Pharma plc ("Horizon") acquired Hyperion Therapeutics, Inc. through a merger. The subject application is a divisional of U.S. Patent No. 8,404,215. The Complaint is provided with an SB-08 filed concurrently herewith.

Respectfully submitted,

By /Lauren L. STEVENS/

Lauren L. Stevens
Attorney for Applicant
Registration No. 36,691
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Electronic Patent Application Fee Transmittal

Application Number:	13610580
Filing Date:	11-Sep-2012
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Lauren Stevens/Valerie Lechner
Attorney Docket Number:	HOR0027-201-US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
			Total in USD ($)	**1400**

Electronic Acknowledgement Receipt

EFS ID:	23024484
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Lauren Stevens/Valerie Lechner
Filer Authorized By:	Lauren Stevens
Attorney Docket Number:	HOR0027-201-US
Receipt Date:	29-JUL-2015
Filing Date:	11-SEP-2012
Time Stamp:	11:13:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1400
RAM confirmation Number	11738
Deposit Account	504297
Authorized User	LECHNER, VALERIE

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

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

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

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		HOR0027_Response.pdf	101545 f728a833ba1f3e47e563364b6e945595082950e7	yes	7
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	7	
Warnings:					
Information:					
2	Notice of concurrent proceedings / decisions	HOR0027_NoticeRelated_Litigation.pdf	91031 38f3b4126982094a78dfda1cfd313e60405e16c3	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30897 5e25a84a085cecfdce1f88660704668e77e28b94	no	2
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Information:					
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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/610,580
				Filing Date	September 11, 2012
Date Submitted: March 12, 2012				**First Named Inventor**	Bruce Scharschmidt
				Art Unit	1629
(use as many sheets as necessary)				**Examiner Name**	Sara Elizabeth Townsley
Sheet	1	of	10	**Attorney Docket Number**	HOR0027-201-US

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
	P1	4,457,942	07-03-1984	Brusilow, S.W.	
	P2	5,654,333	08-05-1997	The United States Of America As Represented By The Department Of Health And Human Services	
	P3	8,094,521	01-10-2012	Nightengale Products LLC	
	P4	8,404,215	03-26-2013	Hyperion Therapeutics, Inc.	
	P5	2003/0195255	10-16-2003	Marshall L. Summar	
	P6	2005/0273359	12-08-2005	Young, D.E.	
	P7	2010/0016207	01-21-2010	Wurtman, RJ et al	
	P8	2014/0142186	05-22-2014	Hyperion Therapeutics, Inc.	
	P9	8,642,012	02-04-2014	Hyperion Therapeutics, Inc.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	F1	WO1994/22494	10-13-1994	The DuPont Merck Pharmaceutical Company		
	F2	WO2013/048558	04-04-2013	Hyperion Therapeutics, Inc.		
	F3	WO2013/158145	10-24-2013	Hyperion Therapeutics, Inc.		

Examiner Signature		Date Considered	

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	D1	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).	
	D2	ANDA Notice Letter, Par Pharmaceutical, Inc. to Hyperion Therapeutics, inc.. Re: Glycerol Phenylbutyrate 1.1 gm/ml oral liquid; United States Patent Nos. 8,404,215 and 8,642,012 Notice of Paragraph IV Certification March 12, 2014.	
	D3	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).	
	D4	Barsotti, Measurement of Ammonia in Blood, 138 J. Pediatrics, S11-S20 (2001)	
	D5	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)	
	D6	Batshaw, M. L. et. al., Alternative Pathway Therapy for Urea Cycle Disorder: Twenty Years Later, 138 J. Pediatrics S46 (2001).	
	D7	Blau, Duran, Blaskovics, Gibson (editors), Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases, 261-276 (2d ed. 1996)	
	D8	BLEI, A. T., et al., "Hepatic Encephalopathy," Am. J. Gastroenterol. 96(7):1968-1976 (2001).	
	D9	Burlina, A.B. et al., Long-Term Treatment with Sodium Phenylbutyrate in Ornithine Transcarbamylase-Deficient Patients, 72 Molecular Genetics and Metabolism 351-355 (2001).	
	D10	Carducci, M., Phenylbutyrate Induces Apoptosis in Human Prostate Cancer and Is More Potent Than Phenylacetate, 2 Clinical Cancer Research 379 (1996).	
	D11	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).	
	D12	Center for Drug Evaluation and Research, Clinical Pharmacology and Biopharmaceutics Review for New Drug Application No. 20-645 (Ammonul®) (2005).	

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	D13	Center for Drug Evaluation and Research, Labeling for New Drug Application No. 20-645 (Ammonul®) (2005).	
	D14	Center for Drug Evaluation and Research, Medical Review for New Drug Application No. 20-645 (Ammonul®) (2005).	
	D15	Chen, Z. et al., Tributyrin: A Prodrug of Butyric Acid for Potential Clinical Application in Differentiation Therapy, 54 Cancer Research 3494 (1994).	
	D16	Clay, A. et. al, Hyperammonemia in the ICU, 132 Chest 1368 (2007).	
	D17	Collins, A.F. et al., Oral Sodium Phenylbutyrate Therapy in Homozygous Beta Thalassemia: A Clinical Trial, 85 Blood 43 (1995).	
	D18	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).	
	D19	CORDOBA, J., "New Assessment of Hepatic Encephalopathy," Journal of Hepatology 54: 1030-1040 (2011).	
	D20	Darmaun, D. et al., Phenylbutyrate-Induced Glutamine Depletion in Humans: Effect on Leucine Metabolism, 5 Am. J. of Physiology: Endocrinology and Metabolism E801 (1998).	
	D21	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).	
	D22	Dixon, M. A. and Leonard, J.V., Intercurrent Illness in Inborn Errors of Intermediary Metabolism, 67 Archives of Disease in Childhood 1387 (1992).	
	D23	Dover, G. et al, Induction of Fetal Hemoglobin Production in Subjects with Sickle Cell Anemia by Oral Sodium Phenylbutyrate, 54 Cancer Research 3494 (1994).	
	D24	Endo, F. et al., Clinical Manifestations of Inborn Errors of the Urea Cycle and Related Metabolic Disorders During Childhood, 134 J. Nutrition 1605S (2004).	

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	D25	European Medicines Agency, Annex I: Summary of Product Characteristics for Ammonaps.	
	D26	European Medicines Agency, European Public Assessment Report: Summary for the Public for Ammonaps (2009).	
	D27	European Medicines Agency, Scientific Discussion for Ammonaps (2005).	
	D28	European Medicines Agency, Scientific Discussion for Carbaglu (2004).	
	D29	FDA Label for Carbaglu, seven pages. (Mar. 2010).	
	D30	Feillet, F. and Leonard, J.V., Alternative Pathway Therapy for Urea Cycle Disorders, 21 J. Inher. Metab. Dis. 101-111 (1998).	
	D31	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).	
	D32	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).	
	D33	Fernandes, Saudubray, Berghe (editors), Inborn Metabolic Diseases Diagnosis and Treatment, 219-222 (3d ed. 2000)	
	D34	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).	
	D35	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).	
	D36	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).	

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	D37	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).	
	D38	Gropman, A.L. et al., Neurological Implications of Urea Cycle Disorders, 30 J. Inherit Metab Dis. 865 (2007).	
	D39	HASSANEIN, T. I., et al., "Randomized Controlled Study of Extracorporeal Albumin Dialysis for Hepatic Encephalopathy in Advanced Cirrhosis," Hepatology 46:1853-1862 (2007).	
	D40	HASSANEIN, T. I., et al., "Introduction to the Hepatic Encephalopathy Scoring Algorithm (HESA)," Dig. Dis. Sci. 53:529-538 (2008).	
	D41	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).	
	D42	Honda, S. et al., Successful Treatment of Severe Hyperammonemia Using Sodium Phenylacetate Power Prepared in Hospital Pharmacy, 25 Biol. Pharm. Bull. 1244 (2002).	
	D43	International Search Report and Written Opinion for PCT/US09/30362, mailed Mar. 2, 2009, 8 pages.	
	D44	International Search Report and Written Opinion for PCT/US2009/055256, mailed Dec. 30, 2009, 13 pages.	
	D45	INTER PARTES REVIEW OF U.S. PATENT NO. 8,404,215 Petition Apr. 29,2015	
	D46	INTER PARTES REVIEW OF U.S. PATENT NO. 8,642,012 Petition Apr. 29,2015	
	D47	Kleppe, S. et al., Urea Cycle Disorders, 5 Current Treatment Options in Neurology 309- 319 (2003).	
	D48	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).	

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Substitute for form 1449/PTO				***Complete if Known***	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/610,580
Date Submitted: March 12, 2012				**Filing Date**	September 11, 2012
				First Named Inventor	Bruce Scharschmidt
				Art Unit	1629
(use as many sheets as necessary)				**Examiner Name**	Sara Elizabeth Townsley
Sheet	6	of	10	**Attorney Docket Number**	HOR0027-201-US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D49	Lee, B. and Goss, J., Long-Term Correction of Urea Cycle Disorders, 138 J. Pediatrics S62 (2001).	
	D50	Lee, B. et al., Considerations in the Difficult-to-Manage Urea Cycle Disorder Patient, 21 Crit. Care Clin. S19 (2005).	
	D51	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, March 22, 2013	
	D52	Leonard, J.V., Urea Cycle Disorders, 7 Semin. Nenatol. 27 (2002).	
	D53	Lizardi-Cervera, J. et al., Hepatic Encephalopathy: A Review, 2 Annals of Hepatology 122-120 (2003).	
	D54	Maestri NE, et al., Prospective treatment of urea cycle disorders. J Paediatr 1991;119:923-928.	
	D55	Maestri, N.E., et al., Long-Term Survival of Patients with Argininosuccinate Synthetase Deficiency, 127 J. Pediatrics 929 (1995).	
	D56	Maestri, N.E., Long-Term Treatment of Girls with Ornithine Transcarbamylase Deficiency, 355 N. Engl. J. Med. 855 (1996).	
	D57	Majeed, K., Hyperammonemia, eMedicine.com (Dec. 2001).	
	D58	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).	
	D59	Matsuda, I., Hyperammonemia in Pediatric Clinics: A Review of Ornithine Transcarbamylase Deficiency (OTCD) Based on our Case Studies, 47 JMAJ 160 (2004).	
	D60	Mizutani, N. et al., Hyperargininemia: Clinical Course and Treatment with Sodium Benzoate and Phenylacetic Acid, 5 Brain and Development 555 (1983).	

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Sheet	7	of	10	**Attorney Docket Number**	HOR0027-201-US

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Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D61	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	
	D62	MOKHTARANI, M., et al., (2012) "Urinary Phenylacetylglutamine as Dosing Biomarker for Patients with Urea Cycle Disorders," Mol Genet Metab 107(3):308-314	
	D63	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.	
	D64	MUNOZ, S. J., "Hepatic Encephalopathy," Med. Clin. N. Am. 92:795-812 (2008).	
	D65	Nassogne, M.C., Urea Cycle Defects: Management and Outcome, 28 J. Inherit. Metab. Dis. 407 (2005).	
	D66	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).	
	D67	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).	
	D68	Newmark, H. L. and Young, W. C., Butyrate and Phenylacetate as Differentiating Agents: Practical Problems and Opportunities, 22 J. Cellular Biochemistry 247 (1995).	
	D69	ORTIZ, M., et al., "Development of a Clinical Hepatic Encephalopathy Staging Scale," Aliment Pharmacol Ther 26:859-867 (2007).	
	D70	PAR PHARMACEUTICAL, INC.'S INITIAL INVALIDITY CONTENTIONS AND NON-INFRINGEMENT CONTENTIONS FOR U.S. PATENT NOS. 8,404,215 AND 8,642,012	
	D71	PARSONS-SMITH, B. G., et al., "The Electroencephalograph in Liver Disease," Lancet 273:867-871 (1957).	

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	D72	Phuphanich, S. et al., Oral Sodium Phenylbutyrate in Patients with Recurrent Malignant Gliomas: A Dose Escalation and Pharmacologic Study, Neuro-Oncology 177 (2005).	
	D73	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).	
	D74	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).	
	D75	SALAM, M., et al., "Modified-Orientation Log to Assess Hepatic Encephalopathy," Aliment Pharmacol Ther. 35(8):913- 920 (2012).	
	D76	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	
	D77	Scottish Medicines Consortium, Carglumic Acid 200 mg Dispersible Tablets (Carbaglu®) No. 299/06 (Sept. 8, 2006).	
	D78	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).	
	D79	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).	
	D80	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).	
	D81	Summar, M., Current Strategies for the Management of Neonatal Urea Cycle Disorders, 138 J. Pediatrics S30 (2001).	
	D82	Summar, M. and Tuchman, M., Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders, 138 J. Pediatrics S6 (2001).	
	D83	Summar, M., Urea Cycle Disorders Overview, Gene Reviews, www.genetests.org (Apr. 2003).	

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	D84	Summar, M. et al., Unmasked Adult-Onset Urea Cycle Disorders in the Critical Care Setting, 21 Crit. Care Clin. S1 (2005).	
	D85	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	
	D86	Todo, S. et al., Orthotopic Liver Transplantation for Urea Cycle Enzyme Deficiency, 15 Hepatology 419 (1992).	
	D87	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).	
	D88	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion dated January 16, 2015 for PCT/US14/58489.	
	D89	UNITED STATES PATENT AND TRADEMARK OFFICE, International Search Report and Written Opinion for PCT/ US2014/060543 dated January 23, 2015.	
	D90	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).	
	D91	Walsh et al., Chemical Abstract vol. 112, No. 231744	
	D92	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).	
	D93	Wilcken, B., Problems in the Management of Urea Cycle Disorders, 81 Molecular Genetics and Metabolism 85 (2004).	
	D94	Wilson, C.J., et al., Plasma Glutamine and Ammonia Concentrations in Ornithine Carbamoyltransferase Deficiency and Citrullinaemia, 24 J. Inherited Metabolic Disease 691 (2001).	
	D95	Wright, G., et al., Management of Hepatic Encephalopathy, 2011 International Journal of Hepatology 1 (2011).	

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	D96	Wright, P., Review: Nitrogen Excretion: Three End Products, Many Physiological Roles, 198 J. Experimental Biology 273 (1995).	
	D97	Yajima, et al. Diurnal Fluctuations of Blood Ammonia Levels in Adult-Type Citrullinemia, 137 Tokohu J. Ex/ Med, 213-220 (1982)	
	D98	Yu, Ryan and Potter, Murray, Diagnosis of Urea Cycle Disorders in Adulthood: Late- Onset Carbamyl Phosphate Synthetase 1 Deficiency, 7 MUMJ 30 (2010).	
	D99	Yudkoff, M. et al., In Vivo Nitrogen Metabolism in Ornithine Transcarbamylase Deficiency, 98 J. Clin. Invest. 2167 (1996).	
	D100	Zeitlin, P., Novel Pharmacologic Therapies for Cystic Fibrosis, 103 J. Clinical Investigation 447 (1999).	
	D101	AHRENS, M. et al. (January 2001). "Consensus Statement From a Conference for the Management of Patients With Urea Cycle Disorders." *Supp. Journal of Pediatrics* 138(1):S1-S5.	
	D102	LEE, B. et al. (August 2008). "Preliminary Data on Adult Patients with Urea Cycle Disorders (UCD) in An Open-Label, Swirch-Over, Dose Escalation Study Comparing a New Ammonia Scavenger, Glyceryl Tri (4-Phenylbutyrate) [HPN-100], to Buphenyl® (Sodium Phenylbutyrate [PBA])", *abstract presented at SSSIEM 2008*, Lisbon, Portugal, one page.	
	D103	LEE, B. et al. (August 2008). "Preliminary Data on Adult Patients with Urea Cycle Disorders (UCD) in An Open-Label, Swirch-Over, Dose Escalation Study Comparing a New Ammonia Scavenger, Glyceryl Tri (4-Phenylbutyrate) [HPN-100], to Buphenyl® (Sodium Phenylbutyrate [PBA])", *presented at SSSIEM 2008*, Lisbon, Portugal, Poster, one page.	

Examiner Signature		Date Considered	

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/30362

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/10; A61K 31/19 (2009.01)
USPC - 514/570
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A01N 37/10; A61K 31/19 (2009.01)
USPC: 514/570

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8): A01N 37/10; A61K 31/19 (2009.01)
USPC: 514/570

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
US WEST(PGPB,USPT,EPAB,JPAB), Google Scholar, Dialog PRO (Engineering)
ammonia scavenging, accumulation, retention, hepatic encephalopathy, urea cycle disorder, phenylacetyl glutamine, PAGN, HPN-100, phenyl butyrate, glyceryl tri-(4-phenyl butyrate)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0229948 A1 (SUMMAR, et al.) 18 November 2004 (18.11.2004), para [0022], [0029], [0035]	1-11, 19-22, 28, 29
Y	US 4,284,647 A (BRUSILOW, et al.) 18 August 1981 (18.08.1981) col 2, ln 26-32; Fig. 3; col 4, ln 35-46.	1-5, 9-18, 23-27, 29
Y	US 5,968,979 A (BRUSILOW) 19 October 1999 (19.10.1999), col 1, ln 27-34; col 1, ln 41-45; col 2, ln 25-34; col 3, ln 3-7; col 3, ln 42-59; col 4, ln 1-26; col 4, ln 54-58; col 5, ln 3-15; ln 29-35	6-29

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 February 2009 (24.02.2009)	02 MAR 2009

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MICHAEL G. SMITH
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE, SUITE 100
SAN DIEGO, CA 92130-2040

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	02 MAR 2009
Applicant's or agent's file reference 643982000140	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 09/30362	07 January 2009 (07.01.2009)	29 April 2008 (29.04.2008)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A01N 37/10; A61K 31/19 (2009.01)
USPC - 514/570

Applicant HYPERION THERAPEUTICS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	24 February 2009 (24.02.2009)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/30362

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Form PCT/ISA/237 (Box No. I) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/30362

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-29	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-29	NO
Industrial applicability (IA)	Claims	1-29	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-5 lack an inventive step under PCT Article 33(3) as being obvious over US 2004/0229948 A1 to Summar, et al. (hereinafter "Summar") in view of US 4,284,647 A to Brusilow, et al. (hereinafter "Brusilow-647").

Regarding claim 1, Summar teaches a method to determine an effective dosage of HPN-100 for a patient in need of treatment for a nitrogen retention disorder, which comprises monitoring the effect of an initial dosage of HPN-100 (para [0022], "glyceryl-tri(4-phenyl butyrate)"; para [0029], "hepatic encephalopathy"; para [0035]). Summar does not teach monitoring the patient's urinary phenylacetyl glutamine (PAGN) output. However, Brusilow-647 teaches a method of determining the patient's urinary PAGN output (col 2, ln 26-32; Fig. 3; col 4, ln 35-46). It would have been obvious to one of ordinary skill in the art to use the method of determining the urinary PAGN output taught in Brusilow-647, in order to determine the effective dosage of HPN-100 for a patient and/or how to adjust the initial dosage of HPN-100 to produce a desired ammonia scavenging effect, as a correlation of phenylacetyl glutamine to phenylacetate administration is disclosed in Brusilow-647 (col 2, ln 26-32), a correlation similar to which would be likely between the administration of HPN-100 and urinary phenylacetyl glutamine output, phenyl acetate being a metabolite of HPN-100 (Summar, para [0005]).

Regarding claim 2, Brusilow-647 further teaches the method of claim 1, wherein urinary PAGN output is determined as a ratio of the concentration of urinary PAGN to urinary creatinine (Fig. 3; col 4, ln 35-46).

Regarding claim 3, Summar further teaches the method of claim 1, wherein the nitrogen retention disorder is chronic hepatic encephalopathy (para [0029]).

Regarding claim 4, Summar further teaches the method of claim 1, wherein administering the effective dosage of HPN-100 to the patient produces a change in plasma ammonia level in the patient (para [0035]). Summar does not explicitly teach achieving normal plasma ammonia levels. However, it would have been obvious to one of ordinary skill in the art to produce normal plasma ammonia levels by administration of HPN-100, as a reduction in plasma ammonium levels following administration of a metabolite of HPN-100, namely phenyl acetic acid, is taught in Brusilow-647 (col 4, ln 46-50; col 4, ln 64-68).

Regarding claim 5, Summar teaches a method to determine an effective dosage of HPN-100 for a patient in need of treatment for a nitrogen retention disorder, which comprises monitoring the effect of an initial dosage of HPN-100 (para [0022], "glyceryl-tri(4-phenyl butyrate)"; para [0029], "hepatic encephalopathy"; para [0035]). Summar does not teach monitoring the patient's urinary phenylacetyl glutamine (PAGN) output. However, Brusilow-647 teaches a method of determining the patient's urinary phenylacetyl glutamine output and total urinary nitrogen (col 2, ln 26-32; Fig. 3; col 4, ln 35-46). It would have been obvious to one of ordinary skill in the art to use the method of determining the urinary phenylacetyl glutamine output taught in Brusilow-647, in order to determine the effective dosage of HPN -100 for a patient and/or how to adjust the initial dosage of HPN-100 to produce a desired ammonia scavenging effect, as a correlation of phenylacetyl glutamine to phenylacetate administration is disclosed in Brusilow-647 (col 2, ln 26-32), a correlation similar to which would be likely between the administration of HPN-100 and urinary phenylacetyl glutamine output, phenyl acetate being a metabolite of HPN-100 (Summar, para [0005]).

Claims 6-8, 19-22 and 28 lack an inventive step under PCT Article 33(3) as being obvious over Summar in view of US 5,968,979 A to Brusilow (hereinafter "Brusilow-979").

Regarding claim 6, Summar teaches a method to determine an effective dosage of HPN-100 for a patient in need of treatment for a nitrogen retention disorder (para [0022], "glyceryl-tri(4-phenyl butyrate)"; para [0029], "hepatic encephalopathy"; para [0035]). Summar does not teach HPN-100 conversion to PAGN. However, Brusilow-979 teaches HPN-100 conversion to PAGN (col 4, ln 1-26, "n = 2"; col 5, ln 3-15; col 5, ln 29-35). It would have been obvious to one of ordinary skill in the art to calculate the dosage of HPN-100 based on a utilization efficiency for HPN-100 conversion into PAGN of about 60% to about 75%, in order to achieve effective plasma concentrations of phenylacetate for acetylation of glutamine, by routine experimentation, as Brusilow-979 teaches the intermediate formation of phenylacetate that produces PAGN by acetylation of glutamine (col 3, ln 3-7).

==========Continued in Supplemental Box==========

Form PCT/ISA/237 (Box No. V) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/30362

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V.2. Citations and Explanations:

Regarding claim 7, Summar (para [0022], [0029], [0035]) and Brusilow-979 (col 4, ln 1-26; col 5, ln 29-35) teach the method of claim 6. Neither Summar nor Brusilow teaches a method wherein the dosage of HPN-100 is calculated from the patient's dietary protein intake. However, it would have been obvious to one of ordinary skill in the art to determine the dosage of HPN-100, in order to effectively deplete accumulated nitrogen via acetylation of glutamine, as taught in Brusilow-979 (col 3, ln 3-7), as the plasma level of glutamine would be likely to depend on the protein intake of the patient, as taught in Brusilow-979 (col 1, ln 41-45).

Regarding claim 8, Summar (para [0022], [0029], [0035]) and Brusilow-979 (col 4, ln 1-26; col 5, ln 29-35) teach the method of claim 7. Neither Summar nor Brusilow-979 teaches a method wherein the dosage of HPN-100 is reduced to account for the patient's residual urea synthesis capacity. However, it would have been obvious to one of ordinary skill in the art to reduce the dosage to account for the patient's residual urea synthesis capacity, by routine experimentation, as urea synthesis would be likely to lesson the plasma nitrogen accumulation, as taught in Brusilow-979 (col 1, ln 27-34).

Regarding claim 19, Brusilow-979 teaches a method to treat a UCD patient with a PBA prodrug, wherein the prodrug produces equivalent or better ammonia level control compared to PBA (col 2, ln 25-34; col 3, ln 42-59, "triglycerides of phenyl alkanoic acid"; col 4, ln 1-26). Brusilow-979 does not teach determining the AUC and Cmax for PBA when the patient receives the PBA prodrug. However, Summar teaches determining the blood levels of phenyl butyrate in a patient (para [0035]). It would have been obvious to one of ordinary skill in the art to determine the effective dosage of the PBA prodrug, in order to treat UCD without the excessive sodium intake associated with administration of phenyl butyrate, as taught in Brusilow-979 (col 2, ln 15-24), by comparing the AUC and Cmax for the prodrug with those when the patient receives an equimolar amount of PBA, by routine experimentation, as the pharmacokinetic parameters would be a measure of the plasma-level of PBA in the patient, measurement of which for determining dosage has been disclosed in Summar (para [0035], "sodium phenyl butyrate and its metabolites").

Regarding claim 20, Brusilow-979 further teaches the method of claim 19, wherein the PBA prodrug is HPN-100 (col 4, ln 1-26, "n = 2").

Regarding claims 21 and 22, Brusilow-979 (col 2, ln 25-34; col 3, ln 42-59) and Summar (para [0035]) teach the method of claim 20. Neither Brusilow nor Summar teaches a method wherein the AUC for PBA exposure is lower with the prodrug than with PBA by at least about 20% or by at least 30%. However, it would have been obvious to one of ordinary skill in the art to expect AUC for PBA exposure to be lower by 20-30% for PBA prodrug than with PBA, in order to treat UCD with minimum exposure to PBA, as taught in Brusilow-979 (col 2, ln 15-24), as the triglyceride of PBA would be likely to produce a stable drug level by gradual beta-oxidation of the prodrug, as taught in Brusilow-979 (col 2, ln 25-34).

Regarding claim 28, Brusilow-979 teaches a method to treat a patient having a nitrogen retention disorder with the PBA prodrug HPN-100 (col 3, ln 42-59, "triglycerides of phenyl alkanoic acid"; col 4, ln 1-26). Brusilow-979 does not teach the AUC or Cmax of PBA. However, Summar teaches determining the blood levels of phenyl butyrate in a patient (para [0035]). It would have been obvious to one of ordinary skill in the art to determine the effective dosage of the PBA prodrug so that AUC for PBA is less than about 600 and the Cmax for PBA is less than about 100 when the PBA prodrug is administered, in order to treat UCD without the excessive sodium intake associated with administration of phenyl butyrate, as taught in Brusilow-979 (col 2, ln 15-24), through routine experimentation, as the pharmacokinetic parameters would be a measure of the plasma-level of PBA in the patient, measurement of which for determining dosage has been disclosed in Summar (para [0035], "sodium phenyl butyrate and its metabolites").

Claims 12-18 and 23-27 lack an inventive step under PCT Article 33(3) as being obvious over Brusilow-647 in view of Brusilow-979.

Regarding claim 12, Brusilow-979 teaches a method to treat a patient having an ammonia retention disorder with a suitable dosage of a PAA prodrug comprising administering to the patient the suitable dosage of the PAA prodrug (col 4, ln 1-26; col 3, ln 56-59). Brusilow-979 does not teach a method of determining the urinary PAGN output of the patient. However, Brusilow-647 teaches a method of determining the urinary PAGN output in a patient (col 2, ln 26-32; Fig 3; col 4, ln 35-46). It would have been obvious to one of ordinary skill in the art to estimate the target urinary PAGN output based on 60-75% convertion of the pro-drug, taking into account the residual urea synthesis capacity and dietary protein intake of the patient, by the method taught in Brusilow-647, in order to determine the amount of the PAA prodrug needed to produce the target amount of urinary PAGN for a patient, as a correlation of urinary PAGN output to the residual urea synthesis capacity and dietary protein intake of the patient and to PAA prodrug administration is disclosed in Brusilow-979 (col 1, ln 27-34; ln 41-45; col 5, ln 3-15; ln 29-35).

Regarding claim 13, Brusilow-979 further teaches the method of claim 12, wherein the PAA prodrug is HPN-100 (col 4, ln 1-26, "n = 2").

Regarding claim 14, Brusilow-979 further teaches the method of claim 12, wherein the PAA prodrug is HPN-100, administered in fewer doses per day (col 3, ln 42-55; col 4, ln 1-26). Brusilow-979 does not teach administering two or three doses of HPN-100 per day. However, it would have been obvious to one of ordinary skill in the art to administer two or three doses of HPN-100 to the patient with clinically significant residual urea synthetic capacity, in order to reduce plasma ammonium to normal levels, as the urea synthetic capacity would be likely to aid in the depletion of nitrogen, as taught in Brusilow-979 (col 1, ln 27-34), thus reducing the number of doses per day of HPN-100 required to be administered to the patient.

==========Continued in Next Supplemental Box==========

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PCT/US 09/30362

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
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Prior Supplemental Box:

Regarding claim 15, Brusilow-979 teaches a method of treatment to a patient comprising substituting HPN-100 for phenylacetate or phenylbutyrate (col 2, ln 25-34; col 3, ln 42-55). Brusilow-979 does not teach a method of determining the urinary PAGN output of the patient. However, Brusilow-647 teaches a method of determining the urinary PAGN output (col 2, ln 26-32; Fig. 3; col 4, ln 35-46). It would have been obvious to one of ordinary skill in the art to transition a patient receiving treatment with an initial amount of phenylacetate or phenylbutyrate to a final amount of HPN-100, by monitoring the amount of urinary PAGN excreted by the patient, in order to assess the effectiveness of the replacement amount of the HPN-100 by the method taught in Brusilow-647, by routine experimentation, as the urinary PAGN output would be a measure of the effectiveness of the waste nitrogen depletion by the drug administered, as taught in Brusilow-647 (col 2, ln 26-32).

Regarding claim 16, Brusilow-979 teaches the method of claim 15 (col 2, ln 25-34; col 3, ln 42-55). Brusilow-979 does not teach determining the urinary PAGN. However, Brusilow-647 teaches a method of determining the urinary PAGN output (col 2, ln 26-32; Fig. 3; col 4, ln 35-46). It would have been obvious to one of ordinary skill in the art to reduce the amount of HPN-100 based on the increase in the amount of urinary PAGN caused by the transition, in order to effectively treat nitrogen-retention disorders, by routine experimentation, as a correlation between urinary PAGN output and HPN-100 is taught in Brusilow-979 (col 5, ln 3-15; ln 29-35).

Regarding claim 17, Brusilow-979 teaches a method of treatment to a patient comprising substituting HPN-100 for phenylacetate or phenylbutyrate (col 2, ln 25-34; col 3, ln 42-55). Brusilow-979 does not teach a method of determining the urinary PAGN output of the patient. However, Brusilow-647 teaches a method of determining the urinary PAGN output (col 2, ln 26-32; Fig. 3; col 4, ln 35-46). It would have been obvious to one of ordinary skill in the art to gradually transition a patient receiving treatment with an initial amount of phenylacetate or phenylbutyrate to a final amount of HPN-100 in small amounts, by monitoring the amount of urinary PAGN excreted by the patient, in order to assess the effectiveness of the replacement amount of the HPN-100 in depleting waste nitrogen as PAGN, by routine experimentation, as the urinary PAGN output would be a measure of the effectiveness of the waste nitrogen depletion by the drug administered, as taught in Brusilow-647 (col 2, ln 26-32).

Regarding claim 18, Brusilow-979 teaches a method of treatment with HPN-100 (col 3, ln 42-55). Brusilow-979 does not teach a method of determining the urinary PAGN output of the patient. However, Brusilow-647 teaches a method of determining the urinary PAGN output (col 2, ln 26-32; Fig. 3; col 4, ln 35-46). It would have been obvious to one of ordinary skill in the art to initiate treatment with HPN-100 in a step-wise fashion and increase the amount of HPN-100 gradually, by monitoring the urinary PAGN based on 60-75% convertion by the method taught in Brusilow-647, taking into account the residual urea synthesis capacity and dietary protein intake of the patient, in order to determine the maintenance dose of HPN-100 effective for the treatment of nitrogen-retention disorders, as a correlation of urinary PAGN output to the residual urea synthesis capacity and dietary protein intake of the patient and HPN-100 administration is disclosed in Brusilow-979 (col 1, ln 27-34; ln 41-45; col 5, ln 3-15; ln 29-35).

Regarding claim 23, Brusilow-647 teaches a method to determine the nitrogen elimination capacity of a patient having a nitrogen retention disorder, being treated with a nitrogen scavenging drug (col 2, ln 26-32; Fig. 3; col 4, ln 35-46, "urinary phenylacetyl glutamine"). Brusilow-647 does not teach a method to determine a suitable dietary protein level for a patient. However, it would have been obvious to one of ordinary skill in the art to use the method taught in Brucilow-647 to determine the patient's endogenous nitrogen elimination capacity with and without the nitrogen scavenging drug, in order to determine the amount of dietary protein the patient can have while being treated with the selected dosage of the nitrogen scavenging drug, through routine experimentation, since the dietary protein intake would be likely to influence the nitrogen elimination capacity of the patient, as taught in Brucilow-979 (col 1, ln 27-34; ln 41-45; col 5, ln 3-15; ln 29-35).

Regarding claim 24, Brusilow-979 further teaches the method of claim 23, wherein the nitrogen scavenging drug is HPN-100 (col 4, ln 1-26, "n = 2").

Regarding claim 25, Brusilow-647 (col 2, ln 26-32; Fig. 3; col 4, ln 35-46) and Brusilow-979 (col 1, ln 27-34; col 1, ln 41-45; col 5, ln 3-15) teach the method of claim 24, wherein Brusilow-979 teaches the selected dosage of HPN-100 (col 4, ln 54-58). Neither Brusilow-647 nor Brusilow-979 teaches a dosage of HPN-100 of up to about 19 grams per day. However, it would have been obvious to one of ordinary skill in the art to determine the dosage of HPN-100 based on the dietary protein the patient intake of the patient, in order to provide effective elimination of waste nitrogen, as PAGN as taught in Brusilow-979 (col 5, ln 3-15), by routine experimentation, as the patient's inherent ability to process nitrogen and the dietary protein intake would be likely to influence the nitrogen elimination capability, measured by the method taught in Brucilow-647 (col 2, ln 26-32; Fig 3; col 4, ln 35-46, "urinary phenylacetyl glutamine").

Regarding claim 26, Brusilow-979 teaches a method to treat a patient with a PBA prodrug, comprising administering HPN-100 to a subject having HE or UCD (col 3, ln 42-59, "triglycerides of phenyl alkanoic acid"; col 4, ln 1-26; col 4, ln 54-58). Brusilow does not teach a daily dose in excess of 19 g per day of the prodrug. However, it would have been obvious to one of ordinary skill in the art to determine the dosage of HPN-100 based on the dietary protein the patient intake of the patient, in order to provide effective elimination of waste nitrogen as PAGN as taught in Brusilow-979 (col 5, ln 3-15), through routine experimentation, since the patient's inherent ability to process nitrogen and the dietary protein intake would likely influence the nitrogen elimination capability, measured by the method taught in Brucilow-647 (col 2, ln 26-32; Fig. 3; col 4, ln 35-46, "urinary phenylacetyl glutamine").

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International application No.
PCT/US 09/30362

Supplemental Box

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

Regarding claim 27, Brusilow-647 (col 2, ln 26-32; Fig. 3; col 4, ln 35-46) and Brusilow-979 (col 1, ln 27-34; col 1, ln 41-45; col 5, ln 3-15) teach the method of claim 26. Neither Brusilow-647 nor Brusilow-979 teaches a daily dose of HPN-100 is between about 199 and about 57 g. However, it would have been obvious to one of ordinary skill in the art to determine the dosage of HPN-100 based on the dietary protein the patient intake of the patient, in order to provide effective elimination of waste nitrogen as PAGN, as taught in Brusilow-979 (col 5, ln 3-15), through routine experimentation, as the patients inherent ability to process nitrogen and the dietary protein intake would likely influence the nitrogen elimination capability, measured by the method taught in Brucilow-647 (col 2, ln 26-32; Fig. 3; col 4, ln 35-46, "urinary phenylacetyl glutamine").

Claims 9-11 and 29 lack an inventive step under PCT Article 33(3) as being obvious over Summar in view of Brusilow-647 and further in view of Brusilow-979.

Regarding claim 9, Summar teaches a method to determine a dosage of a PAA prodrug for a patient having an ammonia retention disorder (para [0022],"glyceryl-tri(4-phenyl butyrate)"; para [0029], "hepatic encephalopathy"; para [0035]). Summar does not explicitly teach determining the patient's residual urea synthesis capacity or dietary intake or estimating the urinary PAGN output. However, Brusilow-647 teaches a method of determining the urinary PAGN output (col 2, ln 26-32; Fig. 3; col 4, ln 35-46). It would have been obvious to one of ordinary skill in the art to estimate the target urinary PAGN output for a patient based on 60-75% convertion of the pro-drug, by the method taught in Brusilow-647, by taking into account the residual urea synthesis capacity and dietary protein intake of the patient, in order to determine the amount of the PAA prodrug needed to produce the target amount of urinary PAGN, as a correlation of urinary PAGN output to the residual urea synthesis capacity and dietary protein intake of the patient and to PAA prodrug administration is disclosed in Brusilow-979 (col 1, ln 27-34; col 1, ln 41-45; col 5, ln 3-15; col 5, ln 29-35).

Regarding claim 10, Summar further teaches the method of claim 9, wherein the PAA prodrug is phenylbutyric acid (PBA) or a pharmaceutically acceptable salt thereof (para [0022]).

Regarding claim 11, Summar further teaches the method of claim 9, wherein the PAA prodrug is HPN-100 (para [0022], "glyceryl-tri(4-phenyl butyrate)").

Regarding claim 29, Brusilow-979 (col 3, ln 42-59, "triglycerides of phenyl alkanoic acid"; col 4, ln 1-26) and Summar (para [0035]) teach the method of claim 28, wherein Summar further teaches that administering the effective dosage of HPN-100 to the patient produces a change in plasma ammonia level in the patient (para [0035]). Neither Brusilow-979 nor Summar explicitly teaches achieving normal plasma ammonia levels. However, it would have been obvious to one of ordinary skill in the art to produce normal plasma ammonia levels by administration of HPN-100, as a reduction in plasma ammonium levels following administration of a metabolite of HPN-100, namely phenyl acetic acid, is taught in Brusilow-647 (col 4, ln 46-50; ln 64-68).

Claims 1-29 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SIMELL O ET AL: "Waste nitrogen excretion via amino acid acylation: Benzoate and phenylacetate in lysinuric protein intolerance" PEDIATRIC RESEARCH, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 20, no. 11, 1 January 1986 (1986-01-01), pages 1117-1121, XP009127277 ISSN: 0031-3998	30-33
Y	the whole document	1-29
	-/--	

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 2009	30/12/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Moreno de Vega, C

International application No
PCT/US2009/055256

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MACARTHUR ROBERT B ET AL: "Pharmacokinetics of sodium phenylacetate and sodium benzoate following intravenous administration as both a bolus and continuous infusion to healthy adult volunteers" MOLECULAR GENETICS AND METABOLISM, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 81, no. Suppl.1, 1 April 2004 (2004-04-01), pages S67-S73, XP009127291 ISSN: 1096-7192 the whole document	1-33
Y	TANNER L M ET AL: "Nutrient intake in lysinuric protein intolerance" JOURNAL OF INHERITED METABOLIC DISEASE, KLUWER ACADEMIC PUBLISHERS, DO, vol. 30, no. 5, 21 June 2007 (2007-06-21), pages 716-721, XP019548954 ISSN: 1573-2665 page 716 - page 717	1-33
X	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))" JOURNAL OF INHERITED METABOLIC DISEASE, KLUWER, DORDRECHT, NL, vol. 31, no. suppl. 1, 1 August 2008 (2008-08-01), page 91, XP009127344 ISSN: 0141-8955	1-5, 15-17, 19-22, 30-33
Y	the whole document	1-33

Electronic Patent Application Fee Transmittal

Application Number:	13610580
Filing Date:	11-Sep-2012
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Lauren Stevens
Attorney Docket Number:	HOR0027-201-US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

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

Electronic Acknowledgement Receipt

EFS ID:	23049641
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Lauren Stevens
Filer Authorized By:	
Attorney Docket Number:	HOR0027-201-US
Receipt Date:	29-JUL-2015
Filing Date:	11-SEP-2012
Time Stamp:	11:16:02
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	11774
Deposit Account	504297
Authorized User	LECHNER, VALERIE

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

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

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

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	HOR0027-201-US_IDS.pdf	154251 569fc23a12b65bdb6c731ec217e44e7297be6b67	no	10
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
2	Foreign Reference	WO9422494A1.pdf	12620304 3c4bf1d6042a077773a3ce513df7225657faf744	no	460
Warnings:					
Information:					
3	Foreign Reference	WO2013048558A2.PDF	1888960 22400ae411d096f1cd99145aeff6b5f3c4c6489b	no	37
Warnings:					
Information:					
4	Foreign Reference	WO2013158145A1.pdf	2539118 0d5a792e8d76a2e55c5cebc1dab781a5c54c6170	no	50
Warnings:					
Information:					
5	Non Patent Literature	Amodio_JHepatol_2008.PDF	10178291 e023c89f552d47a9386de234659c25f7dd3cd110	no	8
Warnings:					
Information:					
6	Non Patent Literature	ANDA_Hyperion.pdf	1828552 353709de30629160d699c3f58bb3c88d5f6cdafb	no	27
Warnings:					
Information:					
7	Non Patent Literature	Bajaj_AlimentPharmacolTher_2011.PDF	525014 814310a71b9c067ca94f43dd2a3740b0f15c3629	no	16
Warnings:					
Information:					

8	Non Patent Literature	Barsotti_2001.pdf	6404000 18d4317a40b5b4c45db7054449ad11294a0e3a40	no	10
Warnings:					
Information:					
9	Non Patent Literature	Batshaw_1975.pdf	3550517 7356b39f946ba4932a55fb3610746c4334dd5377	no	6
Warnings:					
Information:					
10	Non Patent Literature	Batshaw2001.pdf	7711240 f88196bfe6c6d004cef616041a1963ae82c3f909	no	10
Warnings:					
Information:					
11	Non Patent Literature	Blau_1996.pdf	8872480 75669dd767ca3508b04350fcf8366689748d57da	no	20
Warnings:					
Information:					
12	Non Patent Literature	Blei_AmJGastroenterol_2001.PDF	227027 fc3b5ed203fad8fad2619130db53a0de1654fedf	no	9
Warnings:					
Information:					
13	Non Patent Literature	Burlina2001.pdf	3476217 51386f327257d900efbc1dae48eeb7e24d4fb162	no	5
Warnings:					
Information:					
14	Non Patent Literature	Carducci_1996.pdf	7645689 b4e0ffd7dd284384abe7dfa76fed08493a128336	no	10
Warnings:					
Information:					
15	Non Patent Literature	Carducci_2001.pdf	98483 998813a544ae9d14e80123d478b1e7285da772f6	no	9
Warnings:					
Information:					
16	Non Patent Literature	CDER_Ammonaps_Med_Review_Part1.pdf	16640989 a22da4b3c827c27ef62f9b760a170732da23e467	no	27
Warnings:					
Information:					

17	Non Patent Literature	CDER_Ammonaps_Med_Review_Part2.pdf	18000139 762153662643f719d55205ba08374eaaac276d56	no	28
Warnings:					
Information:					
18	Non Patent Literature	Chen_1994.pdf	1364493 19286c62e7e60316a06dad0051f8e9c76e8f578a	no	7
Warnings:					
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19	Non Patent Literature	Clay_2007.pdf	457537 e4d8809a6aa69d116482f352ac8e82da6c2de13c	no	11
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20	Non Patent Literature	Collins_1995.pdf	6098184 4bdad80cf82b7f41501c22e881fdd15fceffc567	no	8
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21	Non Patent Literature	Conn_Gastroenterology_1977.PDF	16141475 e16230f8a97d130ea64df7a190a6bcd80a74c531	no	11
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22	Non Patent Literature	Cordoba_JHepatol_2011.PDF	1646581 8c4c2ac2cbf8b1f5b467e5905969921e800140ca	no	11
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23	Non Patent Literature	Darmaun_1998.pdf	6115821 d45d8b03c974ac017977553df0a080b94a6577fe	no	7
Warnings:					
Information:					
24	Non Patent Literature	CDER_Ammonaps_Label.pdf	12642794 c256d47cc011b7bb52bfcb4cc11837d0532b7f7d	no	20
Warnings:					
Information:					
25	Non Patent Literature	CDER_Ammonaps_CPB.pdf	18572853 020fdbe0556108606fe3dfe5a4dd6ede84a225c5	no	34
Warnings:					
Information:					

26	Non Patent Literature	Diaz_Hepatology_2013.pdf	1115893 66c1600ee308c0eb8c6bad7a907721b6391fba2a	no	16
Warnings:					
Information:					
27	Non Patent Literature	Dixon_1992.pdf	4444752 56719ab372df98c307f5c049926510ae510f282a	no	6
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Information:					
28	Non Patent Literature	Dover_1994.pdf	4221327 9c0f04f904581d0bddfbf4dc8b99deea1d9e06d3	no	5
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Information:					
29	Non Patent Literature	Endo_2004.pdf	3873814 679ad199e147bec455f0e4a8116ac6a5e52430ca	no	5
Warnings:					
Information:					
30	Non Patent Literature	EurMedAgencyAnnex.pdf	16323565 be6351760ffcdae2554c3cb87ea90463262b3a1c	no	33
Warnings:					
Information:					
31	Non Patent Literature	EuroMedAgency_2009.pdf	157626 6ff01398745080dd7a0de135e6e23e61d7fd7617	no	2
Warnings:					
Information:					
32	Non Patent Literature	EurMedAgency_2005.pdf	8935166 f73d78b2269be0a08f292c6182a3a5f266771b3a	no	12
Warnings:					
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33	Non Patent Literature	EurMedAgency_2004.pdf	12768003 fe10fc77402971de1c07b00ea52149425ee1e40f	no	19
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Information:					
34	Non Patent Literature	Feillet_1998.pdf	7152935 e04ce74238c3b463debefe70fa195a1a467e0b3b	no	11
Warnings:					
Information:					

35	Non Patent Literature	FDA_Carbaglu_Label_2010.pdf	2753804 dc59e8d75403150467c1cff9a44ab474868f1bd2	no	7
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Information:					
36	Non Patent Literature	Feoli_Fonseca_1996.pdf	4802821 fdbcbca624b8860f3f8fd454e510b05a767f26f1	no	6
Warnings:					
Information:					
37	Non Patent Literature	Ferenci_Hepatology_2002.pdf	116563 fc1bf6551ecb0dcc4f17fe4e118ea4d16a28122a	no	6
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38	Non Patent Literature	Fernandes_2000.pdf	3678938 c3a3c703d5877ee1da6b6b0f57deacf958090d07	no	8
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Information:					
39	Non Patent Literature	Geraghty_2001.pdf	14402723 799396dfc117dcaaf43e2bcc05ada560f664280b	no	19
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40	Non Patent Literature	GhabrilM_ClinPharmainDrugDev_2013.pdf	290154 fcc71dd56d49e17102c155bce28ea98bd0d8d355	no	7
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41	Non Patent Literature	Gilbert_2001.pdf	8059098 5a769918beaae445c0e630488e9b9f0fbb20735c	no	10
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42	Non Patent Literature	Gore_2001.pdf	8586901 cfbeb00403a5811cef1f9eae9e497719d8f3bc88	no	11
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Information:					
43	Non Patent Literature	Gropman_2007.pdf	17152815 1c0674d3fb3d4a5de4d79fb4a6a53f1c9da20859	no	26
Warnings:					
Information:					

44	Non Patent Literature	Hassanein_AmJGastroenterol_2009.pdf	211886 0847c8721514dd408069540f64a3e34ebdb44834	no	9
Warnings:					
Information:					
45	Non Patent Literature	Hassanein_DigDisSci_2008.pdf	22039102 207cede7e5fb9495559504be5345dc5c0b030290	no	10
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46	Non Patent Literature	Hassanein_Hepatology_2007.pdf	481035 b7d7c14d4993dff95b13bf0ec7fb011d9be9b81c	no	10
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Information:					
47	Non Patent Literature	Honda_2002.pdf	2260511 943208904ac5de712fe58fe4ea1365ede899854c	no	3
Warnings:					
Information:					
48	Non Patent Literature	ISRandWOofISA_PCT_US2009_030362.pdf	469369 bcf873398e7d2e8c77b72a69df12b8a76e5e641e	no	7
Warnings:					
Information:					
49	Non Patent Literature	ISRandWOofISA_PCT_US2009_055256.PDF	101384 01c5c816dea1bdd4c2422b284619853c4f3d3973	no	2
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50	Non Patent Literature	Kleppe_2003.pdf	7683625 768f79f170e1b8e94c6d7b1bf0115e0cffcb2d4a	no	11
Warnings:					
Information:					
51	Non Patent Literature	Kubota_1991.pdf	4739877 5a9fe8b52f5899956970c37939f7bdbabfb7cbbd	no	6
Warnings:					
Information:					
52	Non Patent Literature	Lee_2001.pdf	7977588 d4c375f0e78bf1e1a963e0a75be3378e46fe707b	no	10
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Information:					

53	Non Patent Literature	Lee_2005.pdf	1147552 d77cc970b6e723c473bcd81a81e5830a0cafbcf7	no	9
Warnings:					
Information:					
54	Non Patent Literature	IPR_US8404215_Petition.pdf	589626 e1427bb49e001ec971a224d722f15ad2be77f280	no	68
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Information:					
55	Non Patent Literature	IPR_US8642012_Petition.pdf	546453 d2fb362659177cf0b127473ae7b496c2cbcc1db1	no	68
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Information:					
56	Non Patent Literature	Lee_2013.pdf	76104 96ae17e263d71c8085e19d558cec699beaa893e7	no	2
Warnings:					
Information:					
57	Non Patent Literature	Leonard_2002.pdf	6155259 fe3818002b4c3fcab9c54a4db3efb20cc5dc07dd	no	9
Warnings:					
Information:					
58	Non Patent Literature	Lizardi-CerveraHepatic2Annals2003.pdf	6980 ac633b79c7b082a8cfd497f3193cb162f74dc1c7	no	2
Warnings:					
Information:					
59	Non Patent Literature	MaestriNE_JPediatr_1991.pdf	3965613 b1f57ed403c0ae2135a0c0577b8d5a806baffa1f	no	6
Warnings:					
Information:					
60	Non Patent Literature	Maestri_1995.pdf	2431046 a79699bd040299f284cdaa7dd1dd2b8e7c261794	no	7
Warnings:					
Information:					
61	Fee Worksheet (SB06)	fee-info.pdf	30622 9c50880828a619078213eb2b3008c16c933a8e63	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	345151539

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

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

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

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	13610580
Filing Date	11-Sep-2012
First Named Inventor	Bruce Scharschmidt
Attorney Docket Number	HOR0027-201-US
Title of Invention	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Horizon Therapeutics, Inc.	100%

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

8642012

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted 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 application or any patent issued thereon.
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number 36691 ○ A sole inventor ○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ○ A joint inventor; all of whom are signing this request

Signature	/Lauren Stevens/
Name	Lauren Stevens

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	13610580
Filing Date:	11-Sep-2012
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Lauren Stevens/Valerie Lechner
Attorney Docket Number:	HOR0027-201-US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Statutory or Terminal Disclaimer	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 13610580

Filing Date: 11-Sep-2012

Applicant/Patent under Reexamination: Scharschmidt et al.

Electronic Terminal Disclaimer filed on July 29, 2015

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	23054751
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Lauren Stevens/Valerie Lechner
Filer Authorized By:	Lauren Stevens
Attorney Docket Number:	HOR0027-201-US
Receipt Date:	29-JUL-2015
Filing Date:	11-SEP-2012
Time Stamp:	11:44:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	12117
Deposit Account	504297
Authorized User	LECHNER, VALERIE

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

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

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

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	33376 93148bd6869dee8bd568cf5cd86855537c875b4c	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30586 88349bfcf5da8bc623b10da2fc8cd06b1635ae7c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	63962		

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

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

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

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/610,580	Filing Date 09/11/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **07/29/2015**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 17	Minus	** 40	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					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.

LIE
/EFREM WARREN/

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/610,580	09/11/2012	Bruce Scharschmidt	HOR0027-201-US	1957

101325 7590 05/19/2016

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

EXAMINER	
TOWNSLEY, SARA ELIZABETH	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
05/19/2016	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):

admin@globalpatentgroup.com
vtruman@globalpatentgroup.com
LStevens@horizonpharma.com

Office Action Summary	Application No. 13/610,580	Applicant(s) SCHARSCHMIDT ET AL.	
	Examiner SARA E. TOWNSLEY	Art Unit 1629	AIA (First Inventor to File) Status No

-- 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* MONTHS 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 *7/29/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1,2,5,6 and 9-12* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,2,5,6 and 9-12* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

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

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *7/29/2015*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

FINAL REJECTION

Receipt is acknowledged of Applicants' Amendments and Remarks, filed Jul. 29, 2015.

Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The rejections and/or objections set forth below are either maintained or newly applied, and constitute the complete set presently applied to the instant claims.

STATUS OF THE CLAIMS

Claims 3, 4, 7, 8, and 13 have been cancelled.

Claims 1, 2, 5, 6, 11, and 12 have been amended and incorporate no new matter.

No new claims have been added.

Claims 1, 2, 5, 6, and 9-12 now represent all claims currently pending and under consideration.

INFORMATION DISCLOSURE STATEMENT

The information disclosure statement (IDS) submitted on Jul. 29, 2015 was filed after the mailing date of the non-final action on Feb. 27, 2015. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

TERMINAL DISCLAIMER

The terminal disclaimer filed on Jul. 29, 2015 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of USPN 8,642,012 has been reviewed and is accepted. The terminal disclaimer has been recorded.

MAINTAINED REJECTIONS

The following rejection is maintained from the previous Office Action dated Feb. 27, 2015, on the ground that the references cited therein continue to read on the limitations of the amended claims.

Claim Rejections - 35 USC § 103

Claims 1, 2, 5, 6, and 9-12 stand rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Scharschmidt (US Pub. 2012/0022157) in view of McGuire et al. (*Hepatology* 51, 2077-2085 (2010)).

Independent claim 1 recites a method of treating urea cycle disorders in a subject; and **independent claim 5** recites a method of adjusting the dosage of glyceryl tri-[4-phenylbutyrate], a PAA prodrug, each comprising the steps of

(a) administering a first dosage of glyceryl tri-[4-phenylbutyrate],

(b) measuring plasma PAA and PAGN levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the glyceryl tri-[4-phenylbutyrate] dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range,
where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased, and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and
(e) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] based on the determination in (d).

Scharschmidt discloses the treatment of nitrogen retention disorders, including UCDs (urea cycle disorders), by administering a PAA prodrug, e.g., HPN-100 (para. [0097]), a.k.a. glyceryl tri-[4-phenylbutyrate], as recited by the amended claims.

Scharschmidt discloses methods for determining and adjusting the schedule and dose of orally administered nitrogen scavenging drugs, including glyceryl tri-[4-phenyl-butyrate] (a.k.a. HPN-100 or GPB), based upon the urinary excretion of the drug metabolite phenylacetylglutamine (PAGN) and/or total urinary nitrogen (para. [0021]).

In particular, Scharschmidt discloses methods of (a) administering a first dosage of HPN-100 (glyceryl tri-[4-phenylbutyrate]) (para. [0173]) and (b) measuring urinary PAGN levels (para. [0174]). Scharschmidt further teaches the step of determining whether the PAA prodrug dosage needs to be adjusted based on whether the measured levels of PAGN falls within a target range (paras. [0106], [0174]). Scharschmidt further discloses measuring plasma PAA levels and plasma PAGN levels (Table 4).

Scharschmidt also discloses the step of (e) administering a second dosage of the PAA prodrug based on the determination in (d) (paras. [0106], [0174]).

However, Scharschmidt does not disclose calculating a plasma PAA:PAGN ratio, and comparing the PAA:PAGN ratio to a target range to determine whether the dosage needs to be increased or decreased.

McGuire discloses measuring metabolites in blood and urine after administration of the claimed PAA prodrug, GPB (a.k.a. glyceryl tri-[4-phenylbutyrate]) (abstract), wherein the metabolites include plasma PAA and PAGN (p. 2079, col 2, ¶ 3), which values can easily be compared as a ratio (p. 2081, col. 1, ¶ 2). McGuire further teaches that metabolites important in the monitoring of PAA prodrugs include both PAA and PAGN; and that urinary testing is not as complete and thorough as plasma testing (p. 2081, col. 2, ¶ 1).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Scharschmidt by measuring plasma levels of PAA and PAGN, instead of urinary PAA and PAGN levels, and comparing them as a ratio, in order to more accurately assess the patient's metabolism of PAA prodrugs, e.g., glyceryl tri-[4-phenylbutyrate], and evaluate any need to adjust the dosage, with a reasonable expectation of success, because McGuire teaches that urinary testing is not as complete and thorough as testing for plasma levels of PAA and PAGN.

Independent claim 2 recites a method of treating urea cycle disorders in a subject who has previously been administered a first dosage of a PAA prodrug; and **independent claim 6** recites a method of optimizing the therapeutic efficacy of a PAA

prodrug in a subject who has previously been administered a first dosage of a PAA prodrug, each comprising the steps of

(a) measuring plasma PAA and PAGN levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the first PAA prodrug dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(d) administering a second dosage of the PAA prodrug based on the determination in (c).

Scharschmidt discloses methods of treating urea cycle disorders in a subject who has previously been administered a first dosage of a PAA prodrug (para [0106], [0173]) comprising measuring PAGN levels (para [0174]). Scharschmidt also teaches a method of optimizing the therapeutic efficacy of a PAA prodrug in a subject (para [0297],[0173]) who has previously been administered a first dosage of a PAA prodrug (para [0106]) comprising measuring PAGN levels (para [0174]).

Scharschmidt further teaches the step of determining whether the PAA prodrug dosage needs to be adjusted based on whether the measured levels of PAGN falls within a target range (paras. [0106], [0174]).

Scharschmidt also discloses the step of (d) administering a second dosage of the PAA prodrug based on the determination in (c) (paras. [0106], [0174]).

However, Scharschmidt does not disclose calculating a plasma PAA:PAGN ratio, and comparing the PAA:PAGN ratio to a target range to determine whether the dosage needs to be increased or decreased.

McGuire discloses measuring metabolites in blood and urine after administration of the claimed PAA prodrug, GPB (a.k.a. glyceryl tri-[4-phenylbutyrate]) (abstract), wherein the metabolites include plasma PAA and PAGN (p. 2079, col 2, ¶ 3), which values can easily be compared as a ratio (p. 2081, col. 1, ¶ 2). McGuire further teaches that metabolites important in the monitoring of PAA prodrugs include both PAA and PAGN; and that urinary testing is not as complete and thorough as plasma testing (p. 2081, col. 2, ¶ 1).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Scharschmidt by measuring plasma levels of PAA and PAGN, instead of urinary PAA and PAGN, and comparing them as a ratio, in order to more accurately assess the patient's metabolism of PAA prodrugs, and evaluate any need to adjust (optimize) the dosage, with a reasonable expectation of success, because McGuire teaches that urinary testing is not as complete and thorough as testing for plasma levels of PAA and PAGN.

While Scharschmidt does not disclose that the PAA:PAGN ratio falls within a target range of 1 to 2.5, as recited by claim 9, or within a target range of 1 to 2, as recited by claim 10, it would have been *prima facie* obvious to an ordinarily skilled clinician to determine the optimal target range for the plasma PAA:PAGN ratio for the subject being treated, by routine experimentation.

Scharschmidt further teaches that measuring PAGN levels is carried out after the first dosage of PAA prodrug has had sufficient time to reach steady state (para. [0160]), but does not disclose measurement of both PAA and PAGN levels after the first dosage of PAA prodrug has had sufficient time to reach steady state, as recited by claim 11. However, it would have been *prima facie* obvious to an ordinarily skilled clinician to further measure PAA as well as PAGN in order to maintain comparable results, by routine experimentation.

Scharschmidt further teaches measurement of PAGN levels 48 hours to 1 week after the first dosage of PAA prodrug is administered (para (0160), 3 days), but does not disclose measurement of both PAA and PAGN levels 48 hours to 1 week after the first dosage of PAA prodrug is administered, as recited by claim 12. However, it would have been *prima facie* obvious to an ordinarily skilled clinician to further measure PAA as well as PAGN in order to maintain comparable results, by routine experimentation.

The rationale to combine Scharschmidt and McGuire is premised on the findings that (1) the prior art includes each element claimed, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference; (2) one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately; and (3) one of ordinary skill in the art would have recognized that the results of the combination were predictable.

As recognized by MPEP §2143, combining prior art elements according to known methods to yield predictable results would motivate the skilled artisan to modify the references with a reasonable expectation of success. The rationale to support a conclusion of *prima facie* obviousness is that all the claimed elements were known in the prior art, and a skilled artisan could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. See *KSR Int'l Co. v. Teleflex Inc*. (550 U.S. 398, 409).

RESPONSE TO ARGUMENTS

Applicant's arguments filed Jul. 29, 2015 have been fully considered but they are not persuasive.

With respect to the rejection under 35 U.S.C. § 103, Applicant contends that McGuire describes a statistical approach to assess bioequivalency of 2 different drugs: glycerol phenylbutyrate (GPB) and sodium phenylbutyrate (NaPBA), each of which are metabolized to phenylbutyric acid (PBA). Applicant contends that McGuire compares the ratio of PBA blood levels following administration of GPB with PBA blood levels following administration of NaPBA, wherein the systemic exposure is calculated based on PBA levels taken at multiple time points from multiple patients during dosing with each of the two different drugs. Thus, Applicant contends that McGuire simply utilizes conventional methodology for assessing bioequivalence of one drug to another; McGuire does not teach the novel and unexpected finding that the ratio of two different

metabolites, PAA and PAGN, taken at the same time from the same patient receiving GPB (glyceryl tri-[4-phenylbutyrate]) is of utility in assessing the effectiveness of PAA to PAGN conversion (Remarks, pp. 1-2).

Applicant further contends that nothing in McGuire teaches or suggests measuring two different metabolites from glyceryl tri-[4-phenylbutyrate] in the same patient, and using the ratio of the two metabolites from the same patient to adjust the glyceryl tri-[4-phenylbutyrate] dosage (Remarks, p. 3).

However, McGuire reports two studies. The comparison of the bioequivalence of GPB and NaPBA summarized by Applicant refers to study UP 1204-001; whereas the rejection references study UP 1204-002, in which GPB only was orally administered to 32 subjects (8 healthy and 24 with cirrhosis). The last dose of GPB was administered on day 15, followed by 48 hours of plasma PK sampling and urine collection, and measurement of PAA and PAGN levels, which values are easily compared as a ratio (p. 2079, para. bridging cols. 1-2; Table 2, lower half). McGuire reports that PAA and PAGN predose concentrations increased during the first 2 to 4 days of multiple dosing, but did not increase consistently thereafter, indicating that a steady state had been reached (p. 2082, col. 1; Fig. 3).

In other words, McGuire in fact exemplifies administration of the claimed PAA prodrug, GPB (a.k.a. glyceryl tri-[4-phenylbutyrate]), followed by measuring PAA and PAGN levels in both blood and urine; i.e., measuring two different plasma metabolites from glyceryl tri-[4-phenyl-butyrate] in the same patient.

While it is acknowledged that the cited references do not explicitly disclose that glyceryl tri-[4-phenylbutyrate] dosage can be optimized by comparing plasma metabolite ratios, various methods of optimizing drug dosage regimens are generally known and/or within the capability of those of ordinary skill in the art. In addition, the cited references disclose the active steps of administering glyceryl tri-[4-phenylbutyrate], followed by measuring plasma metabolite levels of PAA and PAGN. Manipulating those values, e.g., by making a comparison or calculation, constitutes a purely mental step, not an active step in carrying out a new method.

For the foregoing reasons, the rejection of claims 1, 2, 5, 6, and 9-12 under 35 U.S.C. § 103 over Scharschmidt and McGuire is maintained.

CONCLUSION

No claims are allowed.

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.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. TOWNSLEY whose telephone number is 571-270-7672. The examiner can normally be reached on Mon-Fri from 9:00 am to 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff S. Lundgren, can be reached at 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SARA E. TOWNSLEY/
Examiner, Art Unit 1629

/JEFFREY S. LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13610580	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SARA E TOWNSLEY	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/05/2014	02/20/2015	05/16/2016						
	1	÷	✓	✓						
	2	÷	✓	✓						
	3	-	-	-						
	4	-	-	-						
	5	÷	✓	✓						
	6	÷	✓	✓						
	7	÷	✓	-						
	8	-	-	-						
	9	÷	✓	✓						
	10	÷	✓	✓						
	11	÷	✓	✓						
	12	÷	✓	✓						
	13	÷	✓	-						

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Scharschmidt et al.

Application No.: 13/610,580

Filing Date: September 11, 2012

For: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

Group Art Unit: 1629

Examiner: Sara Elizabeth Townsley

Docket No.: HOR0027-201-US

Confirmation No.: 1957

RESPONSE TO FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.113

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

Commissioner:

This document is timely filed in response to the Final Office Action mailed May 19, 2016. No additional fees are believed due in connection with this filing, however, should any such fees become due under 37 C.F.R. §§ 1.16 to 1.21 for any reason relating to the instant paper, the Commissioner is authorized to deduct said fees from Global Patent Group, LLC Deposit Account No. 50-4297.

Amendments to the Claims begin on page 2.

Remarks follow the Amendments to the Claims.

AMENDMENTS TO THE CLAIMS

Please amend the claims as follows:

1. (Currently Amended) A method of treating urea cycle disorders in a subject comprising:

(a) administering a first dosage of glyceryl tri-[4-phenylbutyrate],

(b) measuring plasma phenylacetic acid (PAA) and phenylacetyl glutamine (PAGN) levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the glyceryl tri-[4-phenylbutyrate] dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] based on the determination in (d);

wherein the target range is 1 to 2:5.

2. (Currently Amended) A method of treating urea cycle disorders in a subject who has previously been administered a first dosage of glyceryl tri-[4-phenylbutyrate] comprising:

(a) measuring plasma phenylacetic acid (PAA) and phenylacetyl glutamine (PAGN) levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the first dosage of glyceryl tri-[4-phenylbutyrate] needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(d) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] based on the determination in (c);

wherein the target range is 1 to 2:5.

3-4. (Canceled)

5. (Currently Amended) A method of adjusting the dosage of glyceryl tri-[4-phenylbutyrate] comprising:

(a) administering a first dosage of glyceryl tri-[4-phenylbutyrate],

(b) measuring plasma phenylacetic acid (PAA) and phenylacetyl glutamine (PAGN) levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the glyceryl tri-[4-phenylbutyrate] dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] based on the determination in (d);

wherein the target range is 1 to 2:5.

6. (Currently Amended) A method of optimizing the therapeutic efficacy of glyceryl tri-[4-phenylbutyrate] in a subject who has previously been administered a first dosage of glyceryl tri-[4-phenylbutyrate] comprising:

(a) measuring plasma phenylacetic acid (PAA) and phenylacetyl glutamine (PAGN) levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the dosage of glyceryl tri-[4-phenylbutyrate] needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] as necessary based on the determination in (c);

wherein the target range is 1 to 2:5.

7-9. (Canceled)

10. (Previously Presented) The method of any of claims 1, 2, 5, or 6, wherein the target range is 1 to 2.

11. (Previously Presented) The method of any of claims 1, 2, 5, or 6, wherein measurement of PAA and PAGN levels is carried out after the first dosage of glyceryl tri-[4-phenylbutyrate] has

had sufficient time to reach steady state.

12. (Previously Presented) The method of claim 11, wherein measurement of PAA and PAGN levels is carried out 48 hours to 1 week after the first dosage of glyceryl tri-[4-phenylbutyrate] is administered.

13. (Canceled)

REMARKS

Status of Claims

Claims 1, 2, 5, and 6 are amended herein. Claim 9 is canceled herein. No new matter has been added by these amendments. With the entry of this amendment, claims 1, 2, 5, 6, and 10-12 are pending.

Rejections Under 35 U.S.C. § 103(a) (pre-AIA)

The Action rejects claims 1, 2, 5, 6, and 9-12 under 35 U.S.C. § 103(a), as allegedly obvious over Scharschmidt et al. (US 2012/0022157; "Scharschmidt") in view of McGuire et al. (Hepatology 51:2077-85, 2010; "McGuire").

In rejecting independent claims 1 and 5 the Action asserts that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Scharschmidt by measuring plasma levels of PAA and PAGN, instead of urinary PAA and PAGN levels, and comparing them as a ratio, in order to more accurately assess the patient's metabolism of PAA prodrugs, e.g., glyceryl tri-[4-phenylbutyrate], and evaluate any need to adjust the dosage, with a reasonable expectation of success, because McGuire teaches that urinary testing is not as complete and thorough as testing for plasma levels of PAA and PAGN." Action, p. 5. Applicant respectfully disagrees.

The present claims are based on the unexpected observation that the plasma PAA:PAGN ratio provides an accurate measure of PAA prodrug metabolism. *See, e.g.,* Specification as filed, ¶ [0033]. The ratio of an active metabolite, such as PAA, to its terminal metabolite (here, PAGN), would not normally be taken into consideration by the person of ordinary skill in making therapeutic decisions regarding drug dosing. The skilled artisan would expect that higher levels of the active metabolite (PAA) would lead to a proportionately higher response (as measured by PAGN levels) and increased nitrogen waste removal. The results described in the present application demonstrate the surprising and unexpected result that the use of plasma PAA:PAGN ratios to evaluate and adjust PAA prodrug dosage is superior to the use of either PAA or PAGN levels alone.

For example, Figures 2-5 demonstrate the surprising non-linear relationship between

plasma PAA levels and PAA:PAGN ratios in patients at any given time point. When the PAA:PAGN ratio exceeds 1, there is an increase in plasma PAA levels, and at ratios above 2 there is a sharp upswing in plasma PAA levels, with levels of PAA hitting 400 μg/mL or higher. Figures 2A-C. As shown in Table 3, measuring PAA and PAGN and calculating the ratio was predictive of the probability that the patient would subsequently achieve a high level of plasma PAA. Thus, a patient whose PAA:PAGN ratio was greater than 2.5 at 12 hours post-dosing has a 36.4% chance of exceeding 400 mg/mL in plasma PAA sometime during the 24 hour period. Specification as filed, ¶ [0073]. As the specification explains, "basing dose adjustment [] only on a high PAA level without considering concomitant plasma PAGN level may result in unnecessary dose reduction and under-treatment of the patient. Conversely, a PAA level seemingly below the levels associated with toxicity might be taken as an indication of satisfactory dosing without appreciating the fact that the concomitant PAGN level may not be proportional to PAA, indicating that PAA is not being efficiently utilized and may be accumulating." *Id.* at ¶ [0027]. Therapeutically, this is an important discovery not taught or suggested by the prior art. Specifically, once a subject exceeds a specific PAA:PAGN ratio, there is an indication that the active moiety is not being effectively utilized, and increasing the prodrug dosage may actually be deleterious, resulting in accumulation of PAA and associated toxicity. *Id.* at ¶ [0035].

Scharschmidt notes the "evidence that that for certain prodrugs of phenylacetic acid (PAA), measuring the blood level of the prodrug (e.g. PBA [phenylbutyric acid]) or of PAA formed from it is unreliable in assessing drug effect; drug levels in the blood do not correlate with efficacy in this case." Scharschmidt, ¶ [0004]. In particular, Scharschmidt "is based in part on the discovery that bioavailability of these drugs as conventionally assessed based on systemic blood levels of the drugs themselves or of the active species produced in vivo from these drugs does not accurately predict removal of waste nitrogen or reduction of plasma ammonia in healthy human volunteers, adults with liver disease, or patients with UCDs receiving ammonia scavenging drugs." *Id.* at ¶ [0021]. Scharschmidt further explains that, "systemic levels of PAA or PBA are not reliably correlated with the efficacy of HPN-100 as an ammonia scavenger." *Id.* at ¶ [0027].

Scharschmidt observes that "data from three clinical test groups show the inconsistent relationship between plasma PAA and PBA levels among healthy volunteers, patients with cirrhosis and UCD patients, despite the fact that, as described in detail below, all groups exhibited

similar ammonia scavenging activity based on urinary excretion of PAGN." *Id.* at ¶ [0042]. Partly on the basis of those results, Scharschmidt discloses methods of utilizing urinary PAGN levels to determine doses and making dose adjustments of PBA prodrugs such as HPN-100. As such, Scharschmidt teaches away from the use of measured plasma levels of PBA prodrugs or their metabolites for determining dosages and dose adjustment.

The Action also asserts that the teachings in McGuire regarding measuring metabolites, including PAA and PAGN, of PAA prodrugs in plasma, together with the teachings of Scharschmidt, would lead the person of ordinary skill in the art at the time the present invention was made to measure plasma levels of PAA and PAGN in a patient taking a PAA prodrug, and use the PAA/PAGN ratio to adjust the dosage of the PAA prodrug. However, the teaching away of Scharschmidt is not altered by McGuire.

McGuire describes the results of two Phase 1 studies designed to assess safety, tolerability, pharmacokinetic equivalence, and bioequivalence of PBA and GPB (glyceryl phenylbutyrate, HPN-100). McGuire states that PAGN was detectable in the plasma at 24 hours, and therefore urine collection was not complete at 24 hours. On the basis of the pattern of plasma levels and urinary excretion, the urine collection (done for a total of 48 hours) was split into two groups, 0-24 hours and 24-48 hours. McGuire has nothing to say regarding the nature of the sampling, plasma versus urinary, and the correlation of the detected levels of prodrug or metabolite with efficacy of the prodrug as an ammonia scavenger. Rather, McGuire describes safety, tolerability, and bioequivalence.

Nothing in McGuire suggests utilizing PAA:PAGN ratios for therapeutic purposes. McGuire states that "[u]rinary PAGN excretion was significantly greater in all groups after multiple dosing … a result consistent with the larger daily GPB doses and higher plasma PAA and plasma PAGN observed." McGuire, p. 2081, col. 2. McGuire also discloses that, "[u]rinary PAGN is also of particular interest because it is stoichiometrically related to nitrogen scavenging." *Id.* at p. 2084, col. 2. These statements suggest that PAA or PAGN levels alone are sufficient for evaluating and monitoring PAA prodrug dosage, and do not suggest or provide a motivation for calculating PAA:PAGN ratios for these purposes. Therefore, in view of McGuire and the later published Scharschmidt, one of skill in the art would have had the view that urinary PAGN levels, not plasma levels, should be used to assess drug efficacy for purposes of guiding dosing.

Furthermore, the cited references, alone or in combination, fail to teach the target range for the PAA:PAGN ratio is 1 to 2.5 or 1 to 2. The Action acknowledges that "the cited references do not explicitly disclose that glyceryl tri-[4-phenylbutyrate] dosage can be optimized by comparing plasma metabolite ratios," but then vaguely, and generally, asserts that "various methods of optimizing drug dosage regimens are generally known and/or within the capability of those of ordinary skill in the art." Action, p. 11. However, the Action fails to provide any factual evidence in support of a suggestion or motivation in the cited references, alone or in combination, to calculate and utilize the PAA:PAGN ratios described in the present specification, for the purpose of adjusting drug dosage.

In view of the above, the Action has failed to establish a *prima facie* case of obviousness and withdrawal of the rejections is respectfully requested.

Conclusion

In light of the foregoing amendments and arguments, Applicant submits that the application is in condition for allowance and favorable consideration is requested. The Examiner is invited to contact the undersigned by telephone or email if it is felt that an interview would advance the prosecution of the present application.

Respectfully submitted,

/Chris Marion/

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Date: July 7, 2016

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Scharschmidt et al.

Application No.: 13/610,580

Filing Date: September 11, 2012

For: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

Group Art Unit: 1629

Examiner: Sara Elizabeth Townsley

Docket No.: HOR0027-201-US

Confirmation No.: 1957

NOTICE OF RELATED LITIGATION

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

Further to the Notice of Related Litigation filed July 29, 2015, Applicant hereby notifies the U.S. Patent and Trademark Office ("USPTO") that the subject matter of the present application is involved in litigation in the United States.

Specifically, on September 4, 2015, Lupin, Ltd. sent Horizon Therapeutics, Inc. ("Horizon") a letter indicating that Lupin, Ltd. had filed an Abbreviated New Drug Application ("ANDA") with respect to RAVICTI® (Glycerol Phenylbutyrate) Oral Liquid, with a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") alleging that U.S. Patent Nos. 8,404,215 and 8,642,012 are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use or sale of the Lupin, Ltd. drug product. On November 6, 2015, Lupin, Ltd. sent Horizon a second ANDA notice letter indicating that Lupin, Ltd. had also filed a Paragraph IV certification with respect to U.S. Patent No. 9,095,559, issued August 4, 2015.

Under 21 U.S.C. § 355(j)(5)(B)(iii), Horizon had forty-five days from receipt of the first ANDA notice letter to file suit against Lupin, Ltd. for patent infringement. Accordingly, on October 19, 2015, Horizon brought suit on those patents against Lupin, Ltd. and Lupin Pharmaceuticals (collectively, "Lupin") in the United States District Court for the District of

New Jersey. The Complaint alleged that Lupin infringes U.S. Patent Nos. 8,404,215, 8,642,012, and 9,095,559. Horizon subsequently filed an Amended Complaint on April 6, 2016, alleging infringement of only U.S. Patent No. 9,095,559.

On February 9, and May 3, 2016, the USPTO issued U.S. Patent Nos. 9,254,278, and 9,326,966, respectively, which cover RAVICTI® (Glycerol Phenylbutyrate) Oral Liquid. Accordingly, on June 30, 2016, Horizon brought suit against Par Pharmaceutical, Inc. ("Par") in the United States District Court for the District of New Jersey. The Complaint alleged that Par infringes US Patent Nos. 9,095,559, 9,254,278, and 9,326,966.

Respectfully submitted,

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Date: July 7, 2016

Electronic Acknowledgement Receipt

EFS ID:	26286013
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Christopher Lee Marion
Filer Authorized By:	
Attorney Docket Number:	HOR0027-201-US
Receipt Date:	07-JUL-2016
Filing Date:	11-SEP-2012
Time Stamp:	17:46:03
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		20160707_Response.pdf	112949 334467490daddf75ec2fbaa87f55bebe8e665dd9	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	8

Warnings:					
Information:					
2	Miscellaneous Incoming Letter	20160707_NRL.pdf	69502 3b27c8f2baa61867b4269ccfb12014e00a93c314	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	182451		

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 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/610,580	Filing Date 09/11/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **07/07/2016**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 17	Minus	** 40	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					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.

LIE
/DORIS BURNS/

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/610,580	09/11/2012	Bruce Scharschmidt	HOR0027-201-US	1957

101325 7590 07/20/2016

GLOBAL PATENT GROUP - HOR
17014 NEW COLLEGE AVENUE
SUITE 201
WILDWOOD, MO 63040

EXAMINER
TOWNSLEY, SARA ELIZABETH

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
07/20/2016	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):

admin@globalpatentgroup.com
vtruman@globalpatentgroup.com
LStevens@horizonpharma.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 13/610,580	**Applicant(s)** SCHARSCHMIDT ET AL.	
	Examiner SARA E. TOWNSLEY	**Art Unit** 1629	**AIA (First Inventor to File) Status** No

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

THE REPLY FILED 07 July 2016 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

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

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

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

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

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

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

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

NOTICE OF APPEAL

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

AMENDMENTS

3. ☒ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☒ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

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

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

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

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

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

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

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

REQUEST FOR RECONSIDERATION/OTHER

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

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

14. ☐ Other: _____.

STATUS OF CLAIMS

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

Claim(s) allowed: .
Claim(s) objected to: .
Claim(s) rejected: 1,2,5,6 and 9-12.
Claim(s) withdrawn from consideration: .

/Barbara Badio/ Primary Examiner, Art Unit 1628	/SARA E. TOWNSLEY/ Examiner, Art Unit 1629

Continuation of 3. NOTE: Applicant has proposed to amend claims 1, 2, 5, and 6 to recite the limitation "wherein the target range is 1 to 2:5." This limitation was not previously considered, and does not appear to be supported by the instant specification. Thus, further search and consideration would be required.

Continuation of 12. does NOT place the application in condition for allowance because: Applicant's arguments that the newly amended claims are patentable over the prior art references are moot at this time due to non-entry of the proposed amendment..

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Scharschmidt et al.

Application No.: 13/610,580

Filing Date: September 11, 2012

For: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

Group Art Unit: 1629

Examiner: Sara Elizabeth Townsley

Docket No.: HOR0027-201-US

Confirmation No.: 1957

RESPONSE TO FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.113

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

Commissioner:

This document is timely filed in response to the Final Office Action mailed May 19, 2016. No additional fees are believed due in connection with this filing, however, should any such fees become due under 37 C.F.R. §§ 1.16 to 1.21 for any reason relating to the instant paper, the Commissioner is authorized to deduct said fees from Global Patent Group, LLC Deposit Account No. 50-4297.

Amendments to the Claims begin on page 2.

Remarks follow the Amendments to the Claims.

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
HOR0027-201-US	13/610,580	September 11, 2012
First Named Inventor:	**Title:**	
Scharschmidt et al.	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS	

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).
2. The above-identified application contains an outstanding final rejection.
3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.
4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.
5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.
6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).
7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]
8. By filing this certification and request, applicant acknowledges the following:
    - Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
    - The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
        - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
        - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
            - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
            - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	Date
/Chris Marion/	July 29, 2016
Name (Print/Typed)	**Practitioner Registration No.**
Chris L. Marion	L0931

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☑ * Total of 1 forms are submitted.

Privacy Act Statement

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

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Scharschmidt et al.

Application No.: 13/610,580

Filing Date: September 11, 2012

For: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

Group Art Unit: 1629

Examiner: Sara Elizabeth Townsley

Docket No.: HOR0027-201-US

Confirmation No.: 1957

AMENDMENT, RESPONSE TO ADVISORY ACTION, AND AFCP 2.0

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

Commissioner:

This document is timely filed in response to the Advisory Action mailed July 20, 2016. Also filed concurrently herewith is an After Final Consideration Pilot Program 2.0 Request. No additional fees are believed due in connection with this filing, however, should any such fees become due under 37 C.F.R. §§ 1.16 to 1.21 for any reason relating to the instant paper, the Commissioner is authorized to deduct said fees from Global Patent Group, LLC Deposit Account No. 50-4297.

Amendments to the Claims begin on page 2.

Remarks follow the Amendments to the Claims.

AMENDMENTS TO THE CLAIMS

Please amend the claims as follows:

1. (Currently Amended) A method of treating urea cycle disorders in a subject comprising:

(a) administering a first dosage of glyceryl tri-[4-phenylbutyrate],

(b) measuring plasma phenylacetic acid (PAA) and phenylacetyl glutamine (PAGN) levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the glyceryl tri-[4-phenylbutyrate] dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] based on the determination in (d);

wherein the target range is 1 to 2.5.

2. (Currently Amended) A method of treating urea cycle disorders in a subject who has previously been administered a first dosage of glyceryl tri-[4-phenylbutyrate] comprising:

(a) measuring plasma phenylacetic acid (PAA) and phenylacetyl glutamine (PAGN) levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the first dosage of glyceryl tri-[4-phenylbutyrate] needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(d) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] based on the determination in (c);

wherein the target range is 1 to 2.5.

3-4. (Canceled)

5. (Currently Amended) A method of adjusting the dosage of glyceryl tri-[4-phenylbutyrate] comprising:

(a) administering a first dosage of glyceryl tri-[4-phenylbutyrate],

(b) measuring plasma phenylacetic acid (PAA) and phenylacetyl glutamine (PAGN) levels,

(c) calculating a plasma PAA:PAGN ratio,

(d) determining whether the glyceryl tri-[4-phenylbutyrate] dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] based on the determination in (d);

wherein the target range is 1 to 2.5.

6. (Currently Amended) A method of optimizing the therapeutic efficacy of glyceryl tri-[4-phenylbutyrate] in a subject who has previously been administered a first dosage of glyceryl tri-[4-phenylbutyrate] comprising:

(a) measuring plasma phenylacetic acid (PAA) and phenylacetyl glutamine (PAGN) levels,

(b) calculating a plasma PAA:PAGN ratio,

(c) determining whether the dosage of glyceryl tri-[4-phenylbutyrate] needs to be adjusted based on whether the PAA:PAGN ratio falls within a target range, where a PAA:PAGN ratio below the target range indicates that the dosage potentially needs to be increased and a PAA:PAGN ratio above the target range indicates that the dosage needs to be decreased, and

(e) administering a second dosage of the glyceryl tri-[4-phenylbutyrate] as necessary based on the determination in (c);

wherein the target range is 1 to 2.5.

7-9. (Canceled)

10. (Previously Presented) The method of any of claims 1, 2, 5, or 6, wherein the target range

is 1 to 2.

11. (Previously Presented) The method of any of claims 1, 2, 5, or 6, wherein measurement of PAA and PAGN levels is carried out after the first dosage of glyceryl tri-[4-phenylbutyrate] has had sufficient time to reach steady state.

12. (Previously Presented) The method of claim 11, wherein measurement of PAA and PAGN levels is carried out 48 hours to 1 week after the first dosage of glyceryl tri-[4-phenylbutyrate] is administered.

13. (Canceled)

REMARKS

Status of Claims

Entry into the record of the amendment to the claims presented herein, and the remarks previously presented in the Response to Final Office Action filed July 7, 2016, is respectfully requested. Claims 1, 2, 5, and 6 are amended herein. Claim 9 is canceled herein. No new matter has been added by these amendments. With the entry of this amendment, claims 1, 2, 5, 6, and 10-12 are pending.

Comments in Advisory Action

The Advisory Action asserts that amendment to claims 1, 2, 5, and 6, as presented in the Response to the Final Office Action filed July 7, 2016, recites a limitation not previously considered and not supported by the specification. Advisory Action, p. 2. Thus, the Advisory Action asserts that further search and consideration would be required. *Ibid.*

In response, Applicant notes that a typographical error in the previously presented amendment to the claims has been corrected herein. Specifically, recitation of the limitation from now canceled claim 9 was inadvertently presented in amended independent claims 1, 2, 5, and 6 as "wherein the target range is 1 to 2:5" (emphasis added) instead of "wherein the target range is 1 to 2.5" (emphasis added). The amendment to the claims presented herein corrects this typographical error and reference to the remarks related to the rejections under 35 U.S.C. § 103(a) presented in the Response to Final Office Action filed July 7, 2016, is respectfully requested.

Conclusion

In view of the above, entry into the record of the amendments presented herein, and the remarks previously presented in the Response to the Final Office Action filed July 7, 2016, Applicant respectfully submits that all outstanding rejections should be withdrawn and the application allowed. The Examiner is invited to contact the undersigned by telephone or email, if it is felt that an interview would advance the prosecution of the present application.

Respectfully submitted,

/Chris Marion/

Chris L. Marion
Reg. No. L0931
Attorney for Applicant

Global Patent Group, LLC
17014 New College Avenue, Suite 201
Grover, MO 63040
(314) 812-8020

Date: July 29, 2016

Electronic Acknowledgement Receipt

EFS ID:	26486845
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Christopher Lee Marion/Vicki Truman
Filer Authorized By:	Christopher Lee Marion
Attorney Docket Number:	HOR0027-201-US
Receipt Date:	01-AUG-2016
Filing Date:	11-SEP-2012
Time Stamp:	13:03:11
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	After Final Consideration Program Request	20160729_Request_Pilot.pdf	226523 5731019194bba117127e725a528f4c74b0992cd0	no	2

Warnings:

Information:					
2		20160729_Response1.pdf	96967 15ae79d4ffddab90d593fd2211323590d7049586	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	6

Warnings:	
Information:	
Total Files Size (in bytes):	323490

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 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/610,580	Filing Date 09/11/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/01/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 16	Minus	** 40	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						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.

LIE
CAROLYN THOMAS

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/610,580	09/11/2012	Bruce Scharschmidt	HOR0027-201-US	1957

101325 7590 11/03/2016

GLOBAL PATENT GROUP - HOR
17014 NEW COLLEGE AVENUE
SUITE 201
WILDWOOD, MO 63040

EXAMINER	
TOWNSLEY, SARA ELIZABETH	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
11/03/2016	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):

admin@globalpatentgroup.com
vtruman@globalpatentgroup.com
LStevens@horizonpharma.com

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/610,580	SCHARSCHMIDT ET AL.	
	Examiner	Art Unit	
	SARA E. TOWNSLEY	1629	

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

(1) *SARA E. TOWNSLEY*. (3)_____.

(2) *LAUREN STEVENS (Applicant's representative)*. (4)_____.

Date of Interview: *24 August 2016*.

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: *All*.

Identification of prior art discussed: *All*.

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...)

Agreed that the claimed steps of calculating a patient's plasma PAA:PAGN ratio, and adjusting the drug dosage if said ratio lies outside the target range of 1 to 2.5, are not specifically disclosed by the cited references. Discussed whether optimizing the dosage of a drug on the basis of metabolite ratios is routine, in particular with respect to the claimed patient population, which may be inherently limited to infants and children due to the nature of the disease.

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

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

☐ Attachment

/SARA E. TOWNSLEY/ Examiner, Art Unit 1629	/JEFFREY S. LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 13/610,580	**Applicant(s)** SCHARSCHMIDT ET AL.	
	Examiner SARA E. TOWNSLEY	**Art Unit** 1629	**AIA (First Inventor to File) Status** No

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

THE REPLY FILED 01 August 2016 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

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

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

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

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

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

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

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

NOTICE OF APPEAL

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

AMENDMENTS

3. ☐ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

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

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

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

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

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

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

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

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

REQUEST FOR RECONSIDERATION/OTHER

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

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

14. ☒ Other: PTO-2323 and interview summary attached.

STATUS OF CLAIMS

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

Claim(s) allowed: .
Claim(s) objected to: .
Claim(s) rejected: 1,2,5,6 and 10-12.
Claim(s) withdrawn from consideration: .

/JEFFREY S. LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629	/SARA E. TOWNSLEY/ Examiner, Art Unit 1629

Continuation of 12. does NOT place the application in condition for allowance because: Applicant's arguments filed Jul. 7, 2016 and Aug. 1, 2016 have been fully considered but they are not persuasive.

With respect to the rejection under 35 U.S.C. § 103(a), Applicant contends that a prima facie case of obviousness has not been established because the cited references fail to disclose, teach, or suggest methods of adjusting the dosage of glyceryl tri-[4-phenylbutyrate] ("GPB") by measuring the plasma levels of GPB's active metabolite, PAA, and its terminal metabolite, PAGN; calculating the plasma PAA:PAGN ratio; and determining whether said ratio falls within the target range of 1 to 2.5, as recited by independent claims 1, 2, 5, and 6, or 1 to 2, as recited by dependent claim 10. Applicant contends that the instant claims are based on the unexpected finding that the plasma PAA:PAGN ratio provides an accurate measure of GPB metabolism, which is superior to previously known methods of adjusting GPB dosage based on one of PAA or PAGN levels alone (Remarks, p. 5).

However, on the basis of Mayo Collaborative Services v. Prometheus Laboratories Inc., 132 S. Ct. 1289 (U.S. 2012), the claimed steps of "calculating" a plasma PAA:PAGN ratio, and "determining" whether the GPB dosage needs to be adjusted based on whether the PAA:PAGN ratio falls within the target range of 1 to 2.5, are not given patentable weight, for the following reasons.

The claims at issue in Mayo are nearly identical to the instant claims. Prometheus was the sole and exclusive licensee of the two patents at issue, which concerned the use of thiopurine drugs to treat autoimmune diseases. When ingested, the body metabolizes the drugs, producing metabolites in the bloodstream. Because patients metabolize these drugs differently, doctors have found it difficult to determine whether a particular patient's dose is too high, risking harmful side effects, or too low, and so likely ineffective. Prometheus' claims set forth processes embodying researchers' findings that identified correlations between metabolite levels and likely harm or ineffectiveness with precision. Each claim recited (1) an "administering" step, instructing a doctor to administer the drug to a patient; (2) a "determining" step, telling the doctor to measure the resulting metabolite levels in the patient's blood; and (3) a "wherein" step, describing the metabolite concentrations above which there is a likelihood of harmful side-effects and below which it is likely that the drug dosage is ineffective, i.e., a target range.

The Court held that such claims are directed to laws of nature or natural phenomena and as such are not patent eligible. The relationships between concentrations of certain metabolites in the blood and the likelihood that a drug dosage will prove ineffective or cause harm are not themselves patentable. The three additional steps were not themselves natural laws, but were also insufficient to transform the nature of the claims, because they were conventional and well known.

The "determining" step tells a doctor to measure patients' metabolite levels, through whatever process the doctor wishes to use. Because methods for making such determinations were well known in the art, this step simply tells doctors to engage in well-understood, routine, conventional activity. Such activity is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law. In telling a doctor to measure metabolite levels and to consider the resulting measurements in light of the correlations they describe, the claimed methods would tie up subsequent treatment decisions, and threaten to inhibit the development of more refined treatment recommendations that combine the claimed correlations with later discoveries.

Here, the cited references establish that the remaining steps recited by the instant claims - administering a first dosage of GPB to a patient with a urea cycle disorder, measuring the plasma levels of PAA and PAGN, and administering a second dosage of GPB - were routine, conventional steps which were known in the art.

For the foregoing reasons, the rejection under 35 U.S.C. § 103 is maintained.
.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/610,580	SCHARSCHMIDT ET AL.	
	Examiner	Art Unit	
	SARA E. TOWNSLEY	1629	

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

(1) *SARA E. TOWNSLEY*. (3)_____.

(2) *LAUREN STEVENS (Applicant's representative)*. (4)_____.

Date of Interview: *24 August 2016*.

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: *All*.

Identification of prior art discussed: *All*.

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...)

Agreed that the claimed steps of calculating a patient's plasma PAA:PAGN ratio, and adjusting the drug dosage if said ratio lies outside the target range of 1 to 2.5, are not specifically disclosed by the cited references. Discussed whether optimizing the dosage of a drug on the basis of metabolite ratios is routine, in particular with respect to the claimed patient population, which may be inherently limited to infants and children due to the nature of the disease.

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

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

☐ Attachment

/SARA E. TOWNSLEY/ Examiner, Art Unit 1629	/JEFFREY S. LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629

AFCP 2.0 Decision	Application No.	Applicant(s)
	13/610,580	SCHARSCHMIDT ET AL.
	Examiner	Art Unit
	SARA E. TOWNSLEY	1629

This is in response to the After Final Consideration Pilot request filed 01 August 2016.

1. **Improper Request** – The AFCP 2.0 request is improper for the following reason(s) and the after final amendment submitted with the request will be treated under pre-pilot procedure.

   ☐ An AFCP 2.0 request form PTO/SB/434 (or equivalent document) was not submitted.

   ☐ A non-broadening amendment to at least one independent claim was not submitted.

   ☐ A proper AFCP 2.0 request was submitted in response to the most recent final rejection.

   ☐ Other:

2. **Proper Request**

   A. After final amendment submitted with the request will not be treated under AFCP 2.0.
   The after final amendment cannot be reviewed and a search conducted within the guidelines of the pilot program.

   ☐ The after final amendment will be treated under pre-pilot procedure.

   B. Updated search and/or completed additional consideration.
   The examiner performed an updated search and/or completed additional consideration of the after final amendment within the time authorized for the pilot program. The result(s) of the updated search and/or completed additional consideration are:

   ☐ 1. All of the rejections in the most recent final Office action are overcome and a Notice of Allowance is issued herewith.

   ☒ 2. The after final amendment would not overcome all of the rejections in the most recent final Office action. See attached interview summary for further details.

   ☐ 3. The after final amendment was reviewed, and it raises a new issue(s). See attached interview summary for further details.

   ☐ 4. The after final amendment raises new issues, but would overcome all of the rejections in the most recent final Office action. A decision on determining allowability could not be made within the guidelines of the pilot. See attached interview summary for further details, including any newly discovered prior art.

   ☐ 5. Other:

   Examiner Note: Please attach an interview summary when necessary as described above.

OK TO ENTER: /S.E.T./ 08/24/2016

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Scharschmidt et al.

Application No.: 13/610,580

Filing Date: September 11, 2012

For: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

Group Art Unit: 1629

Examiner: Sara Elizabeth Townsley

Docket No.: HOR0027-201-US

Confirmation No.: 1957

AMENDMENT, RESPONSE TO ADVISORY ACTION, AND AFCP 2.0

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

Commissioner:

This document is timely filed in response to the Advisory Action mailed July 20, 2016. Also filed concurrently herewith is an After Final Consideration Pilot Program 2.0 Request. No additional fees are believed due in connection with this filing, however, should any such fees become due under 37 C.F.R. §§ 1.16 to 1.21 for any reason relating to the instant paper, the Commissioner is authorized to deduct said fees from Global Patent Group, LLC Deposit Account No. 50-4297.

Amendments to the Claims begin on page 2.

Remarks follow the Amendments to the Claims.

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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

Application Number	13610580	Filing Date	2012-09-11	Docket Number (if applicable)	HOR0027-201-US	Art Unit	1629
First Named Inventor	Scharschmidt, Bruce			Examiner Name	Townsley, Sara Elizabeth		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C. 371, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV.

SUBMISSION REQUIRED UNDER 37 CFR 1.114

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

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

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

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

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

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 504297

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Chris Marion/	Date (YYYY-MM-DD)	2016-11-18
Name	Chris Marion	Registration Number	L0931

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

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

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

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

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

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

Electronic Patent Application Fee Transmittal

Application Number:	13610580
Filing Date:	11-Sep-2012
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Christopher Lee Marion
Attorney Docket Number:	HOR0027-201-US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
RCE- 1st Request	1801	1	1200	1200
		Total in USD ($)		**6740**

Electronic Acknowledgement Receipt

EFS ID:	27559525
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Christopher Lee Marion
Filer Authorized By:	
Attorney Docket Number:	HOR0027-201-US
Receipt Date:	18-NOV-2016
Filing Date:	11-SEP-2012
Time Stamp:	16:19:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$6740
RAM confirmation Number	112116INTEFSW00003221504297
Deposit Account	504297
Authorized User	Valerie Lechner

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

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		20161118_Response.pdf	91419 7234c7f391015bb21cb7451f040dbcabafd27f20	yes	4

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Response After Final Action	1	1
Claims	2	3
Applicant Arguments/Remarks Made in an Amendment	4	4

Warnings:					
Information:					
2	TrackOne Request	20161118_Track_1.pdf	124867 e239c1124c5d9b63fbd8865c900902f27a745904	no	2
Warnings:					
Information:					
3	Request for Continued Examination (RCE)	20161118_RCE.pdf	1349885 3fc1a47e15f5797694fc921e580e4b3ca5f0c947	no	3
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	39332 fceecc16c18a4adafa45c03d29b24387fe2fd210	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1605503		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Scharschmidt et al.

Application No.: 13/610,580

Filing Date: September 11, 2012

For: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

Group Art Unit: 1629

Examiner: Sara Elizabeth Townsley

Docket No.: HOR0027-201-US

Confirmation No.: 1957

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

AMENDMENT, RESPONSE TO ADVISORY ACTION, AND REQUEST FOR CONTINUED EXAMINATION

Commissioner:

This document is timely filed in response to the Advisory Action mailed November 3, 2016, and the Final Office Action dated May 19, 2016. Also filed concurrently herewith is a Request for Continued Examination. No additional fees are believed due in connection with this filing, however, should any such fees become due under 37 C.F.R. §§ 1.16 to 1.21 for any reason relating to the instant paper, the Commissioner is authorized to deduct said fees from Global Patent Group, LLC Deposit Account No. 50-4297.

Amendment to the Claims begins on page 2.

Remarks follow the Amendments to the Claims.

AMENDMENT TO THE CLAIMS

Please amend the claims as follows:

1-13. (Canceled)

14. (New) A method of treating a urea cycle disorder in a subject in need thereof, the method comprising:

(a) administering a first dosage of glyceryl tri-[4-phenylbutyrate] to the subject, wherein the first dosage results in a ratio of plasma phenylacetic acid (PAA) to phenylacetylglutamine (PAGN) greater than 2 in the subject; and

(b) administering a second dosage of glyceryl tri-[4-phenylbutyrate] to the subject, wherein the second dosage is less than the first dosage.

15. (New) The method of claim 14, further comprising measuring the PAA level and the PAGN level in the subject after administering the first dosage and reaching a steady state of glyceryl tri-[4-phenylbutyrate] in the subject.

16. (New) The method of claim 14, further comprising measuring the PAA level and the PAGN level in the subject about 48 hours to about one week after the first dosage is administered to the subject.

17. (New) A method of treating a urea cycle disorder in a subject in need thereof, the method comprising:

(a) administering a first dosage of glyceryl tri-[4-phenylbutyrate] to the subject, wherein the first dosage results in a ratio of plasma phenylacetic acid (PAA) to phenylacetylglutamine (PAGN) greater than 2.5 in the subject; and

(b) administering a second dosage of glyceryl tri-[4-phenylbutyrate] to the subject, wherein the second dosage is less than the first dosage.

18. (New) The method of claim 17, further comprising measuring the PAA level and the PAGN level in the subject after administering the first dosage and reaching a steady state of glyceryl tri-[4-phenylbutyrate] in the subject.

19. (New) The method of claim 17, further comprising measuring the PAA level and the PAGN level in the subject about 48 hours to about one week after the first dosage is administered to the subject.

20. (New) A method of treating a urea cycle disorder in a subject in need thereof, the method comprising:

(a) administering a first dosage of glyceryl tri-[4-phenylbutyrate] to the subject, wherein the first dosage results in a ratio of plasma phenylacetic acid (PAA) to phenylacetylglutamine (PAGN) less than 1 in the subject; and

(b) administering a second dosage of glyceryl tri-[4-phenylbutyrate] to the subject, wherein the second dosage is greater than the first dosage.

21. (New) The method of claim 20, further comprising measuring the PAA level and the PAGN level in the subject after administering the first dosage and reaching a steady state of glyceryl tri-[4-phenylbutyrate] in the subject.

22. (New) The method of claim 20, further comprising measuring the PAA level and the PAGN level in the subject about 48 hours to about one week after the first dosage is administered to the subject.

REMARKS

Status of Claims

Claims 1-13 are canceled and claims 14-22 are added. Support for the amendment to the claims can be found in the specification. No new matter has been added by these amendments. With the entry of this amendment, claims 14-22 are pending.

Reference to the remarks related to the rejections under 35 U.S.C. § 103(a) presented in the Response to Final Office Action filed July 7, 2016, is respectfully requested.

Conclusion

In view of the above, entry into the record of the amendments presented herein, and the remarks previously presented in the Response to the Final Office Action filed July 7, 2016, Applicant respectfully submits that all outstanding rejections should be withdrawn and the application allowed. The Examiner is invited to contact the undersigned by telephone or email, if it is felt that an interview would advance the prosecution of the present application.

Respectfully submitted,

/Chris Marion/

Chris L. Marion
Reg. No. L0931
Attorney for Applicant

Global Patent Group, LLC
17014 New College Avenue, Suite 201
St. Louis, MO 63040
(314) 812-8020

Date: November 18, 2016

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Scharschmidt, Bruce	Nonprovisional Application Number (if known):	13/610,580
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Chris Marion/	Date 2016-11-18
Name (Print/Typed) Chris Marion	Practitioner Registration Number L0931

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

Privacy Act Statement

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

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

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

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/610,580	Filing Date 09/11/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **11/18/2016**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 9	Minus	** 20	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					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.

LIE
GOIGA DUCKETT

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
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GLOBAL PATENT GROUP - HOR
17014 NEW COLLEGE AVENUE
SUITE 201
WILDWOOD MO 63040

MAILED
NOV 28 2016
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/610,580

1. THE REQUEST FILED November 18, 2016 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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NOTICE OF ALLOWANCE AND FEE(S) DUE

101325 7590 12/16/2016

GLOBAL PATENT GROUP - HOR
17014 NEW COLLEGE AVENUE
SUITE 201
WILDWOOD, MO 63040

EXAMINER
TOWNSLEY, SARA ELIZABETH

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 12/16/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/610,580	09/11/2012	Bruce Scharschmidt	HOR0027-201-US	1957

TITLE OF INVENTION: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	03/16/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

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

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

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

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

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

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

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

PART B - FEE(S) TRANSMITTAL

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

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

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

101325 7590 12/16/2016
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SUITE 201
WILDWOOD, MO 63040

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/610,580	09/11/2012	Bruce Scharschmidt	HOR0027-201-US	1957

TITLE OF INVENTION: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	03/16/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
TOWNSLEY, SARA ELIZABETH	1629	514-533000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

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

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/610,580	09/11/2012	Bruce Scharschmidt	HOR0027-201-US	1957

101325 7590 12/16/2016

GLOBAL PATENT GROUP - HOR
17014 NEW COLLEGE AVENUE
SUITE 201
WILDWOOD, MO 63040

EXAMINER	
TOWNSLEY, SARA ELIZABETH	
ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 12/16/2016

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

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

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

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

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

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

Notice of Allowability	Application No. 13/610,580	Applicant(s) SCHARSCHMIDT ET AL.	
	Examiner SARA E. TOWNSLEY	Art Unit 1629	AIA (First Inventor to File) Status No

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

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

1. ☒ This communication is responsive to *Applicant's reply filed Nov. 18, 2016*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *14 and 17*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

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

   * Certified copies not received: _____.

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

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

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

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20161208* .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SARA E. TOWNSLEY/ Examiner, Art Unit 1629	/JEFFREY S. LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629

EXAMINER'S AMENDMENT

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

Authorization for this examiner's amendment was given in an interview with Applicant's representative, Lauren Stevens, on Dec. 8, 2016.

The application has been amended as follows:

Claims 15, 16, and 18-22 are canceled.

Claim 14 is amended in its entirety as follows:

A method of treating a urea cycle disorder in a subject comprising administering to a subject having a plasma PAA to PAGN ratio outside the target range of 1 to 2, a dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) effective to achieve a plasma PAA to PAGN ratio within the target range of 1 to 2.

Claim 17 is amended in its entirety as follows:

A method of treating a urea cycle disorder in a subject comprising administering to a subject having a plasma PAA to PAGN ratio outside the target range of 1 to 2.5, a dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) effective to achieve a plasma PAA to PAGN ratio within the target range of 1 to 2.5.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. TOWNSLEY whose telephone number is (571)270-7672. The examiner can normally be reached on Mon - Fri, 9:00 am - 5:00 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff S. Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARA E. TOWNSLEY/
Examiner, Art Unit 1629

/JEFFREY S. LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/610,580	SCHARSCHMIDT ET AL.	
	Examiner	Art Unit	
	SARA E. TOWNSLEY	1629	

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

(1) *SARA E. TOWNSLEY*. (3)_____.

(2) *LAUREN STEVENS (Applicant's representative)*. (4)_____.

Date of Interview: *08 December 2016*.

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: *All*.

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...)

Agreed to amend independent claims 14 and 17 to overcome potential issues under 35 U.S.C. 112, and to cancel claims 15, 16, and 18-22.

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

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

☐ Attachment

/SARA E. TOWNSLEY/ Examiner, Art Unit 1629	/JEFFREY S. LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13610580	SCHARSCHMIDT ET AL.
	Examiner	Art Unit
	SARA E TOWNSLEY	1629

CPC- SEARCHED		
Symbol	Date	Examiner
A61K31/192	12/9/2016	set
A61K31/216	12/9/2016	set

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
61/636,256 considered	2/20/2015	set
Inventor name/assignee search (PALM, EAST)	2/20/2015	set
EAST keyword search (USPAT, PGPub, USOCR, EPO, JPO, Derwent)	2/20/2015	set
Patentability conference (Jeff Lundgren)	12/9/2016	set

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/192	12/9/2016	set
A61K	31/216	12/9/2016	set

/SARA E TOWNSLEY/ Examiner, Art Unit 1629	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13610580	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SARA E TOWNSLEY	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/05/2014	02/20/2015	05/16/2016	12/08/2016					
	1	÷	✓	✓	-					
	2	÷	✓	✓	-					
	3	-	-	-	-					
	4	-	-	-	-					
	5	÷	✓	✓	-					
	6	÷	✓	✓	-					
	7	÷	✓	-	-					
	8	-	-	-	-					
	9	÷	✓	✓	-					
	10	÷	✓	✓	-					
	11	÷	✓	✓	-					
	12	÷	✓	✓	-					
	13	÷	✓	-	-					
1	14				=					
	15				-					
	16				-					
2	17				=					
	18				-					
	19				-					
	20				-					
	21				-					
	22				-					

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13610580	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SARA E TOWNSLEY	1629

CPC						
Symbol					**Type**	**Version**
A61K		31	/	192	F	2013-01-01
A61K		31	/	216	I	2013-01-01
G01N		33	/	6812	I	2013-01-01
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CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

/SARA E TOWNSLEY/ Examiner.Art Unit 1629	12/9/2016	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	2	
/JEFFREY S LUNDGREN/ Supervisory Patent Examiner.Art Unit 1629	12/12/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13610580	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SARA E TOWNSLEY	1629

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
514	533

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	570				

INTERNATIONAL CLASSIFICATION																
CLAIMED						NON-CLAIMED										
A	6	1	K	31 / 192 (2006.01.01)												
A	6	1	K	31 / 216 (2006.01.01)												
A	6	1	K	31 / 225 (2006.01.01)												

/SARA E TOWNSLEY/ Examiner.Art Unit 1629	12/9/2016	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	2	
/JEFFREY S LUNDGREN/ Supervisory Patent Examiner.Art Unit 1629	12/12/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13610580	SCHARSCHMIDT ET AL.
	Examiner	**Art Unit**
	SARA E TOWNSLEY	1629

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	14														
2	17														

/SARA E TOWNSLEY/ Examiner.Art Unit 1629 (Assistant Examiner)	12/9/2016 (Date)	**Total Claims Allowed:** 2	
/JEFFREY S LUNDGREN/ Supervisory Patent Examiner.Art Unit 1629 (Primary Examiner)	12/12/2016 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

PART B - FEE(S) TRANSMITTAL

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

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

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

101325 7590 12/16/2016
GLOBAL PATENT GROUP - HOR
17014 NEW COLLEGE AVENUE
SUITE 201
WILDWOOD, MO 63040

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

VIA EFS-WEB	(Depositor's name)
	(Signature)
12/22/2016	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/610,580	09/11/2012	Bruce Scharschmidt	HOR0027-201-US	1957

TITLE OF INVENTION: METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	03/16/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
TOWNSLEY, SARA ELIZABETH	1629	514-533000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Horizon Therapeutics, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Lake Forest, IL

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 50-4297 (enclose an extra copy of this form).

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

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Chris Marion/ Date December 22, 2016

Typed or printed name Chris Marion Registration No. L0931

Electronic Patent Application Fee Transmittal

Application Number:	13610580
Filing Date:	11-Sep-2012
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Filer:	Christopher Lee Marion/Valerie Lechner
Attorney Docket Number:	HOR0027-201-US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	27887112
Application Number:	13610580
International Application Number:	
Confirmation Number:	1957
Title of Invention:	METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS
First Named Inventor/Applicant Name:	Bruce Scharschmidt
Customer Number:	101325
Filer:	Christopher Lee Marion/Valerie Lechner
Filer Authorized By:	Christopher Lee Marion
Attorney Docket Number:	HOR0027-201-US
Receipt Date:	22-DEC-2016
Filing Date:	11-SEP-2012
Time Stamp:	18:11:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$960
RAM confirmation Number	122316INTEFSW00006220504297
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1	Issue Fee Payment (PTO-85B)	HOR0027_IssueFeeTransmittal.pdf	92962 f689fee6c0632232c341be6d6c50f9902388b7dc	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30716 ea2208971312a1d1db213b290d181fd527993314	no	2
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New Applications Under 35 U.S.C. 111

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

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/610,580	02/07/2017	9561197	HOR0027-201-US	1957

101325 7590 01/18/2017

GLOBAL PATENT GROUP - HOR
17014 NEW COLLEGE AVENUE
SUITE 201
WILDWOOD, MO 63040

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 649 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

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

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

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

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

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