IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.,
Petitioner,

v.

HORIZON THERAPEUTICS, LLC,
Patent Owner.

Case IPR: Unassigned
U.S. Patent No. 9,561,197

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,561,197 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.1-.80, 42.100-.123

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1002	Declaration of Neal Sondheimer, M.D., Ph.D.
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1004	Lee, B., *et al.*, *Phase 2 Comparison of a Novel Ammonia Scavenging Agent with Sodium Phenylbutyrate in Patients with Urea Cycle Disorders: Safety, Pharmacokinetics and Ammonia Control*, MOLECULAR GENETICS METABOLISM, 100: 221-28 (2010) ("Lee")
1005	Praphanphoj, V., *et al.*, *Three Cases of Intravenous Sodium Benzoate and Sodium Phenylacetate Toxicity Occurring in the Treatment in the Treatment of Acute Hyperammonaemia*, J. INHERIT. METAB. DIS., 23: 129-36 (2000) ("Praphanphoj")
1006	Thibault, A., *et al.*, *A Phase I and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer*, CANCER RESEARCH, 54: 1690-94 (1994) ("Thibault")
1007	Carducci, M.A., *et al.*, *A Phase I Clinical and Pharmacological Evaluation of Sodium Phenylbutyrate on an 120-h Infusion Schedule*, CLINICAL CANCER RESEARCH, 7: 3047-55 (2001) ("Carducci")
1008	Msall, M., *et al.*, *Neurologic Outcome in Children with Inborn Errors of Urea Synthesis — Outcome of Urea-Cycle Enzymopathies*, NEW ENGLAND JOURNAL OF MEDICINE, 310: 1500-05 (1984)
1009	File History for U.S. Patent No. 9,561,197
1010	MacArthur, R.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, 81: S67-S73 (2004)
1011	McGuire, B.M., *et al.*, *Pharmacology and Safety of Glycerol Phenylbutyrate in Healthy Adults and Adults with Cirrhosis*, HEPATOLOGY, 51: 2077-85 (2010)
1012	Buxton, I.L.O., *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 1-39 (L. Brunton et al., eds., 11th ed. 2006)

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1013	Ravicti Product Label, Revised: Apr. 2017
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1015	Ammonul Label, Revised: Feb. 2005
1016	Center for Drug Evaluation and Research, NDA No. 203284, Summary Review
1017	Feillet, F. and Leonard, J.V., *Alternative Pathway Therapy for Urea Cycle Disorders*, J. INHER. METAB. DIS., 21: 101-11 (1998).
1018	Fernandes, J., *et al.*, *Inborn Metabolic Diseases Diagnosis and Treatment*, 214-222 (J. Fernandes et al., eds., 3d ed. 2000)
1019	Scientific Discussion for Ammonaps, EMEA, 1-12 (2005)
1020	Scharschmidt, B., U.S. Patent Appl. Pub. No. 2010/0008859 (filed Jan. 7, 2009; published Jan. 14, 2010)
1021	Scharschmidt, B., U.S. Patent Appl. Pub. No. 2012/0022157 (filed Aug. 27, 2009; published Jan. 26, 2012)
1022	Brusilow, *Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion*, PEDIATRIC RESEARCH, 29: 147-50 (1991)
1023	Brusilow, S.W., U.S. Patent No. 5,968,979 (filed Jan. 13, 1998; issued Oct. 19, 1999)
1024	Yang, D., *et al.*, *Assay of the Human Liver Citric Acid Cycle Probe Phenylacetylglutamine and of Phenylacetate in Plasma by Gas Chromatography-Mass Spectrometry*, ANALYTICAL BIOCHEMISTRY, 212: 277-82 (1993)
1025	Yamaguchi, M. and Nakamura, M., *Determination of Free and Total Phenylacetic Acid in Human and Rat Plasma by High-Performance Liquid Chromatography with Fluorescence Detection*, CHEM. PHARM. BULL., 35: 3740-45 (1987)
1026	Laryea, M.D., *et al.*, *Simultaneous LC-MS/MS Determination of Phenylbutyrate, Phenylacetate Benzoate and their Corresponding Metabolites Phenylacetylglutamine and Hippurate in Blood and Urine*, J. INHERITED METABOLIC DISEASES, 33: S321-S328 (2010)

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1027	Ravicti Orange Book Entry, *available at* https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=203284&Appl_type=N (last accessed June 19, 2018)
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1032	*Biochemistry*, 426-59 (Reginald H. Garrett & Charles M. Grisham, eds., 2nd ed. 1999)

I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Par Pharmaceutical, Inc. submits this Petition for *Inter Partes* Review ("IPR") seeking cancellation of claims 1 and 2 of U.S. Patent No. 9,561,197 (EX1001) as unpatentable under 35 U.S.C. § 103(a).

In patients with urea cycle disorders ("UCDs"), the clinical benefit of glyceryl tri-[4-phenylbutyrate] ("GPB") derives from the ability of GPB to metabolize into phenylacetic acid ("PAA")[1], which conjugates with nitrogen to form phenylacetylglutamine ("PAGN") and replace urea as a vehicle for carrying waste nitrogen out of the body. (EX1001, 2:58-62.) This conjugation avoids the buildup of toxic ammonia in patients with defective urea cycle functionality. (*Id.*)

The challenged claims generally recite methods of administering a dose of GPB in an amount effective to achieve a specific ratio of PAA to PAGN in the subject's plasma, in subjects whose PAA:PAGN plasma ratio is outside a specific

[1] The '197 patent defines PAA as "phenylacetic acid." (EX1001, 2:4-10, 2:38-55.) A person of ordinary skill in the art ("POSA") would understand that "phenylacetic acid" encompasses either phenylacetic acid or its conjugate base, phenylacetate. (EX1002, ¶5 n.1.) As used herein, PAA means either phenylacetic acid or phenylacetate.

range. (*Id.*, 32:9-20.) But in doing so, the '197 patent merely claims the long-known concept of a therapeutic window, and is, thus, not inventive.

First, GPB dosages that result in a plasma PAA:PAGN ratio below the low end of the target range, i.e., PAA:PAGN values <1, were recognized in the art as being less than effective because the PAA levels need to be sufficiently high in order to be available for conjugation with glutamine. Second, GPB dosages that result in a plasma PAA:PAGN ratio above the high end of the target range, i.e., PAA:PAGN values >2 (or >2.5), were recognized in the art as being too high because such PAA levels result in undesirable PAA-dependent toxicity. Therefore, the doses of GPB that achieve safe and effective amounts of PAA were well-known in the art.

More particularly, the prior art disclosed every part of the challenged claims. For instance, GPB was a well-known pro-drug of PAA used to control ammonia levels in patients with UCDs. GPB was also known to be preferable over the standard UCD treatment with sodium phenylbutyrate[2] ("NaPBA") because: (1) GPB provides the same amount of active ingredient in a smaller dose (four

[2] A POSA would understand that "phenylbutyric acid" refers to phenylbutyric acid and/or its conjugate base, phenylbutyrate. (EX1002, ¶5 n.1.) As used herein, PBA refers to phenylbutyric acid and/or phenylbutyrate.

teaspoonfuls instead of forty tablets); (2) decreases the amount of sodium intake for patients; (3) avoids the unpleasant taste of NaPBA; and (4) and provides PAA at a more constant level. Lee (EX1004), for example, disclosed these aspects of GPB treatment well-before the '197 patent. Lee also taught that UCD patients with a mean plasma PAA:PAGN ratio of about 0.52, did not have proper ammonia control. To that end, prior art such as Praphanphoj disclosed that a patient properly treated with PAA had an initial PAA plasma level of 462.4 μg/mL that decreased to 204 μg/mL, resulting in a plasma PAA:PAGN ratio range of 1.7-4.5, with the initial elevation of PAA:PAGN due to the delayed onset of PAA's conversion to PAGN.

Further, high plasma PAA levels were well-known to cause neurotoxicity and even death. For example, Thibault (EX1006) noted reversible neurotoxicity at PAA plasma concentrations of 906 μg/mL and higher. And Praphanphoj reported that two patients died after receiving inadvertent overdoses of PAA that resulted in plasma PAA values in excess of 1000 μg/mL and plasma PAA:PAGN ratios of 13.7 and 14.4. (EX1005, 130-133.)

Lastly, PAA's conversion to PAGN was well-known to be saturable, which leads to PAA buildup and toxicity. For instance, Carducci (EX1007) found that the maximum PAGN plasma level achieved from continuous infusion of various dosages of PAA was ~320 μg/mL. Taken together with Thibault's report of

toxicity at a PAA plasma level of 906 μg/mL, a POSA would have understood that PAA toxicity could begin to appear at a plasma PAA:PAGN ratio of around 2.8 due to PAA's buildup and lack of conversion to PAGN. Thus, a POSA would have expected the benefit of increasing the dose of GPB would be increased PAA plasma levels, but that such benefit would become outweighed by PAA's toxicity at around the point of saturation of PAA to PAGN conversion.

The challenged claims merely apply known techniques to a known method of using GPB to treat UCDs, achieving predictable results; as illustrated in this petition and evidenced by the supporting Declaration of Dr. Neal Sondheimer (EX1002), an internationally-renowned expert in the genetic causes, diagnosis, and treatment of UCDs. Each of the challenged claims, therefore, are fatally obvious under the Supreme Court's *KSR* decision and its extensive progeny. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). Further, no publicly available evidence of objective indicia of nonobviousness weighs in favor of patentability. Accordingly, as explained in detail below, Par is reasonably likely to prevail with respect to each of the challenged claims.

II. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Par certifies that the '197 patent is available for IPR and Par is not barred or estopped from requesting IPR of any of the challenged claims.

III. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE

The Office should institute IPR under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80 and 42.100-42.123, and cancel claims 1 and 2 of the '197 patent as unpatentable under pre-AIA 35 U.S.C. § 103(a) for the reasons explained below. Par's detailed, full statement of the reasons for relief requested is provided in Section VI.

IV. OVERVIEW

A. POSA

A POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the '197 patent, a POSA would have been a physician with an M.D. and specialized training in the diagnosis and treatment of inherited metabolic disorders, such as UCDs and other nitrogen retention disorders. (EX1002, ¶17.) Today, such a person may also have post-graduate training to fulfill the requirements of the American Board of Medical Genetics and Genomics in Clinical Genetics, Clinical Biochemical Genetics, or Medical Biochemical Genetics. (*Id.*)

Before April 20, 2012,[3] a POSA would have been aware of the teachings provided by the references discussed in this Petition and by Dr. Sondheimer, who also discusses prior art teachings confirming the general knowledge of a POSA. *See Abbott Labs. v. Andrx Pharm., Inc.*, 452 F.3d 1331, 1336 (Fed. Cir. 2006) (stating that a person of ordinary skill possesses the "understandings and knowledge reflected in the prior art"); *see also Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) ("[T]he knowledge of [a person of ordinary skill in the art] is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious"). A POSA, based on then existing literature, would also have had general knowledge of the methods used to diagnose and treat UCDs. (EX1002, ¶17.)

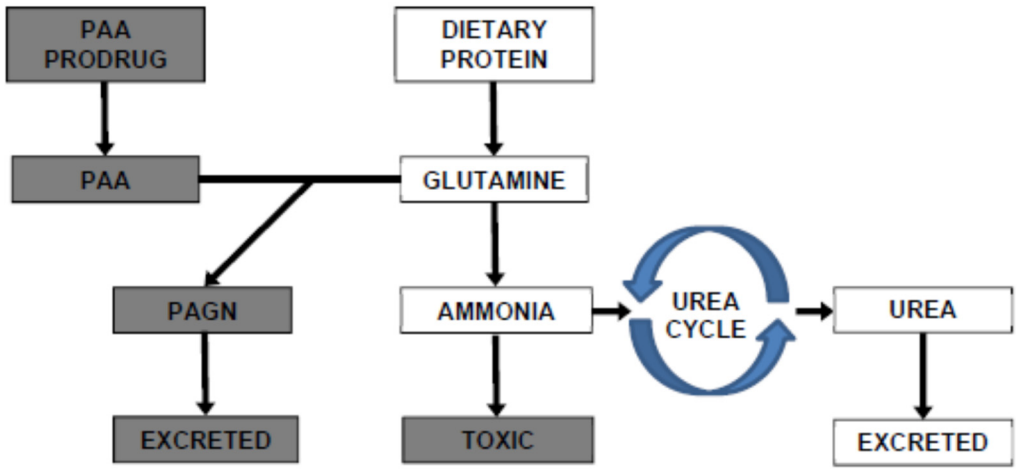
B. Scope and Content of the Prior Art Before April 20, 2012

1. The Urea Cycle and UCDs

Protein is an essential part of everybody's diet. Most people can consume a reasonable excess of protein without any adverse health problems. The body metabolizes dietary protein into amino acids. In healthy people, excess amino acids (such as glutamine) are metabolized into, among other things, waste nitrogen

[3] Par does not concede that the '197 patent is entitled to an effective filing date of April 20, 2012, rather that it is not entitled to any earlier date.

in the form of ammonia.[4] (EX1017, 101-02; EX1018, 214; EX1002, ¶¶19-20.) The action of enzymes then processes that ammonia into urea, via the urea cycle. (EX1017, 101; EX1004, 221; EX1002, ¶19.) The body readily eliminates urea through urine. (EX1017, 102; EX1002, ¶19.) The following schematic figure illustrates how the urea cycle contributes to the elimination of ammonia, following the unshaded pathway:

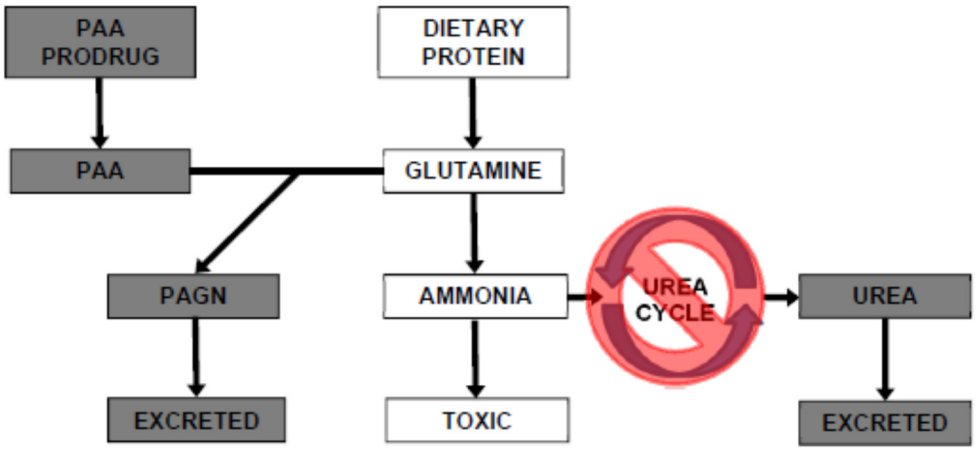


(EX1002, ¶20.)

The urea cycle is the major pathway for the metabolism and excretion of waste nitrogen. (EX1017, 101; EX1002, ¶19.) UCDs occur in newborn, child, and adult patients due to deficient enzymes or transporters in the urea cycle, often due to genetic conditions. (EX1001, 1:19-47; EX1017, 102-03; EX1018, 215-17;

[4] Excess amino acids refer to amino acids beyond those necessary for ordinary bodily functions. (EX1002, ¶20.)

EX1002, ¶19.) A breakdown in the urea cycle significantly reduces the body's ability to process excess ammonia, leading to elevated plasma ammonia levels and hyperammonemia. (EX1008, 1500; EX1019, 1; EX1002, ¶¶19, 21.) The following figure illustrates how a disorder in the urea cycle causes toxic ammonia to build up in the unshaded pathway:



(EX1002, ¶21.) Ammonia results in toxicity to the body's nerve cells. Thus, prolonged or severe hyperammonemia can cause lethargy, coma, irreversible brain defects and death. (EX1008, 1500; EX1019, 1; EX1002, ¶19.)

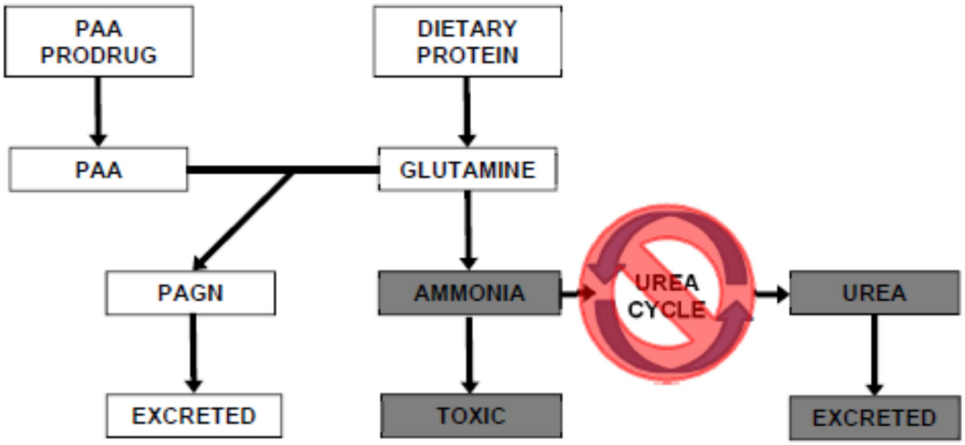
2. Nitrogen Scavenging Drugs

In addition to diet modifications, the prior art standard of care was to administer nitrogen scavenging drugs to patients having UCDs. (EX1014, 1; EX1018, 219; EX1002, ¶23.) Such drugs were known, and were primarily based on the archetypical nitrogen scavenging drug, PAA.

a. PAA and PBA

In the body, PAA conjugates to glutamine to form PAGN, which can be easily eliminated through urine. (EX1014, 1; EX1020, ¶22; EX1002, ¶23.) Each molecule of glutamine converted to PAGN removes two nitrogen atoms that would form two molecules of toxic ammonia. (EX1020, ¶¶22-23; EX1002, ¶23.)

One drawback of PAA is its offensive odor. (EX1022, 147; EX1002, ¶24.) Therefore, NaPBA, a prodrug of PAA[5], was developed. In 1996, Horizon began marketing NaPBA under the brand name Buphenyl. (EX1014; EX1002, ¶24.) The body rapidly metabolizes NaPBA to PAA after its administration. (EX1014, 1; EX1002, ¶24.) The following figure illustrates this process and how it was known in the prior art that PAA and PAA-prodrugs, such as NaPBA, remove free glutamine and thereby reduce the risk of toxic ammonia build-up in a UCD patient:



[5] PAA-prodrugs are drugs that the body metabolizes into to PAA after administering the PAA-prodrug to a subject. (EX1002, ¶14 n.2.)

(EX1002, ¶23.) NaPBA was also known to have certain drawbacks. (*Id.*, ¶24.) For instance, NaPBA was typically administered in the form of forty 0.5g tablets per day. (EX1023, 3:48-51; EX1002, ¶24.) This results in an intake of approximately 2363 mg of sodium, in addition to the UCD patient's sodium intake through his or her diet, which can be excessive in view of the recommended daily intake of 1500 and 2300 mg/day for sodium in individuals with hypertension and the general population, respectively. (EX1004, 222; EX1002, ¶24.)

b. GPB

A few years after development of NaPBA, the pre-prodrug GPB was developed, a.k.a. HPN-100–the drug recited in the Asserted Claims–which is made up of three PBA molecules esterified to one glycerol molecule. (EX1004, 222; EX1020, ¶23; EX1023, 4:66-5:2; EX1002, ¶25.) After GPB administration, pancreatic lipases cleave the PBA from GPB; the released PBA then metabolizes into PAA. (EX1004, 224; EX1002, ¶25.) GPB was known to overcome the limitations of PBA and PAA by (1) providing the same amount of active ingredient in a smaller dose (four teaspoonfuls instead of forty tablets), (2) decreasing the amount of sodium intake for patients, (3) avoiding PBA's unpleasant taste, and (4) providing the active component of the drug at a more constant level. (EX1020, ¶65; EX1023, 3:48-55; EX1004, 222, 224; EX1002, ¶26.)

3. PAA Was Known to Cause Neurotoxicity At High Levels.

The prior art also disclosed that high plasma levels of PAA resulted in neurotoxicity and even death. (EX1002, ¶27.) For example, Thibault reported that following continuous infusions of PAA in cancer patients,[6] reversible neurotoxicity due to PAA accumulation was observed:

> Drug-related toxicity was clearly related to the serum phenylacetate concentration. Three episodes of CNS toxicity, limited to confusion and lethargy and often preceded by emesis, occurred in patients treated at dose levels 3 and 4. They were associated with drug concentrations of 906, 1044, and 1285 μg/mL (1078 ± 192 μg/mL), respectively.

(EX1006, 1693; EX1002 ¶27.) Praphanphoj reported that two patients died after receiving inadvertent overdoses of PAA that resulted in plasma PAA values in excess of 1000 μg/mL.[7] (EX1005, Summary, Table 1; EX1002, ¶28.)

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[6] As discussed herein, a POSA would expect PAA toxicity in cancer patients and UCD patients alike. (*See* Section VI.A.2.; EX1002, ¶60.) As such, PAA toxicity reported in studies on cancer patients would have been relevant to a POSA developing a method of dosing GPB to UCD patients that avoids PAA-dependent toxicity. (*See* Section VI.A.2.; EX1002, ¶60.)

[7] The PAA and PAGN values reported in Praphanphoj are in units of mmol/L, which have been converted to μg/mL, herein. (EX1002, ¶28 n.3.) The molecular

FDA-approved labels for commercially-available, prior art nitrogen scavenging drugs used in UCD patients contained warnings about PAA toxicity. For example, the Buphenyl label states: "Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate, 250-300 mg/kg/day for 14 days, repeated at 4-week intervals." (EX1014, 3-4; EX1002 ¶29.) The Ammonul label cites to Thibault to report the exact same information. (EX1015, 8; EX1002, ¶29.)

In fact, the prior art recommends "maintaining the plasma levels of phenylacetate . . . below the levels associated with toxicity, while providing enough of these scavenging agents to maximize waste nitrogen removal" and also changing the dosing to "lessen the risk of attaining inappropriately high plasma phenylacetate [PAA] levels, while maximizing its conversion to PAG[N]." (EX1010, S72; EX1002, ¶34.)

Moreover, a POSA would have understood the concept of the therapeutic window, which is an important principal of medical pharmacology. (EX1002, ¶36.) "[A] therapeutic window . . . reflect[s] a concentration range that provides efficacy without unacceptable toxicity." (EX1012, 18 (emphasis removed); EX1002, ¶36.) This concept is graphically depicted below, which relates the

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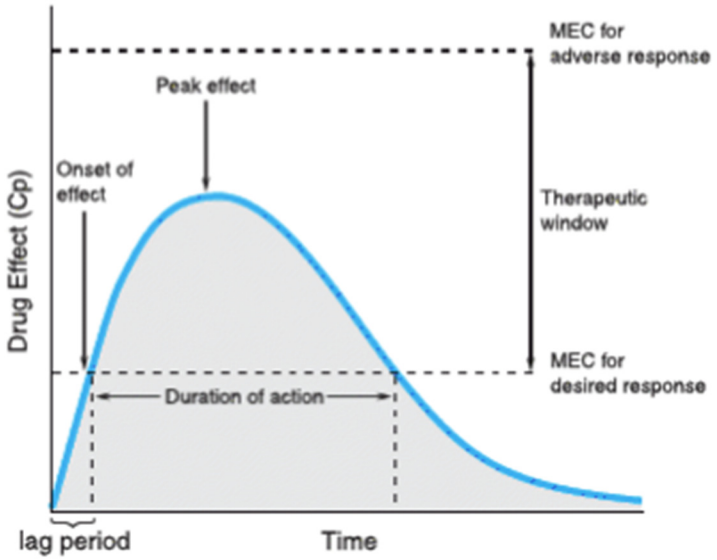
weight of PAA is 136.15 g/mol. (EX1028, 1; EX1002, ¶28 n.3.) The molecular weight of PAGN is 264.3 g/mol. (EX1029, 1; EX1002, ¶30 n.5.)

plasma drug concentration (Cp) to the minimum effective concentration (MEC) for both desired and adverse responses. (EX1012, 19; EX1002, ¶36.)



As such, a POSA's "therapeutic goal is to obtain and maintain concentrations within the therapeutic window for the desired response with a minimum of toxicity." (EX1012, 19; EX1002, ¶37.) Accordingly, the core concept of the '197 patent claims merely applies the well-understood concept that some concentrations of PAA would be undesirably low because of poor effectiveness, some would have been desirable, and some would have been unacceptable due to toxicity. (EX1002, ¶37.)

In addition, the art reported various methods for determining plasma PAA and PAGN levels. (*See generally* EX1024; EX1025; EX1002, ¶35.) For instance, Laryea et al. taught that "[k]nowledge regarding concentrations of . . . PAA[] and PBA and their metabolite[] . . . PAG[N] in urine and blood is a prerequisite for

detailed studies on their metabolism and for pharmacokinetic and evaluation studies." (EX1026, S322; EX1002, ¶35.) Laryea also disclosed that "individual dosage and therapy optimization are highly important in children with inborn errors of urea synthesis." (EX1026, S322; EX1002, ¶35.) Further, Laryea concluded that his method provided "rapid, accurate, and clinically useful means of monitoring the therapeutic course." (EX1026, S327; EX1002, ¶35.) As such, a POSA would have readily been able to measure a patient's plasma PAA:PAGN ratio and would have had a reason to do so in order to determine GPB's therapeutic window. (EX1002, ¶¶35-37.)

4. PAA's Conversion to PAGN Was Known to Be Saturable.

By April 20, 2012, PAA's known toxicity would also have been a concern to a POSA because it was known that the metabolic step that converts PAA to PAGN can become saturated, leading to unwanted accumulation of PAA in the body. (EX1002, ¶¶30-33.) For example, MacArthur et al. reported that "[t]he clearance of phenylacetate appears to be much slower and . . . can become saturated at the plasma levels attained with doses used to treat hyperammonemia." (EX1010, S72; EX1002, ¶32.)

Carducci reported PAA accumulation in one out of four patients dosed with PBA at a rate of 76.87 μmol/h/kg and four out of six patients dosed with 91.35 μmol/h/kg. (EX1007, 3052; EX1002, ¶30.) And Carducci concluded that

"[i]n any individual whose V_{max} is less than his or her drug-dosing rate, PA[A] can be expected to accumulate progressively."[8] (EX1007, 3052; EX1002, ¶30.) Carducci further reported that the maximum PAGN plasma level achieved from continuous infusion of 515 mg/kg/d PBA was ~320 µg/mL,[9] and PAA's conversion to PAGN was, thus, saturable. (EX1007, Figure 2; EX1002, ¶30.) Carducci noted that a patient whose PAGN plasma level plateaued experienced grade 3 neuro-cortical toxicity that reversed 10-12 hours after discontinuation of PBA dosing. (EX1007, 3051; EX1002, ¶30.)

Thibault also reported the "saturable pharmacokinetics of phenylacetate." (EX1006, 1693-94; EX1002, ¶31.) In fact, Thibault taught that PAA has nonlinear pharmacokinetics with the K_m of PAA, i.e., the concentration at which the conversion of PAA to PAGN is half-maximal, being only 105 µg/mL, showing the limited ability of PAA to convert to PAGN at higher concentrations. (EX1006, Abstract, 1692-93; EX1032, 437; EX1002, ¶31.) A POSA would have, therefore, recognized the limited ability of PAA to convert to PAGN at higher concentrations because this K_m concentration is relevant to the plasma concentrations seen in

[8] V_{max} represents the maximum rate of an enzymatic reaction. (EX1032, 434-37.)

[9] Carducci reports that PAGN plateaued at ~1200-1250 µmol/L, i.e., ~317-330 µg/mL. (EX1007, Figure 2; EX1002, ¶30 n.5.)

therapeutic use of PAA-prodrugs. (EX1002, ¶31.) And a POSA would have expected PAA's efficacy in removing waste nitrogen could not be increased once there was saturation of PAA's conversion to PAGN. (*Id.*, ¶33.)

C. Summary of the '197 Patent

1. Brief Description of the '197 Patent

Against this background, Scharschmidt and Mokhtarani filed a patent application, which issued as the '197 patent on February 7, 2017, providing methods of treating UCDs by measuring a patient's plasma PAA to PAGN ratio and adjusting the dose of GPB administered to the patient based on that ratio. The '197 patent asserts its earliest priority claim to April 20, 2012. According to the Office's electronic assignment records, Horizon Therapeutics, LLC ("Horizon") owns the '197 patent by assignment.

2. The '197 Patent Claims

The '197 patent has two issued claims, each of which is independent. Claim 1 is reproduced below:

> 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.

(EX1001, 32:9-14.) Claim 2 is substantially similar to claim 1, except it recites a "target range of 1 to 2.5." (*Id.*, 32:15-20.)

3. Prosecution Background and Summary of Arguments

As originally filed, the application that issued as the '197 patent contained independent claims generally reciting methods of treating a nitrogen retention disorder by measuring a subject's plasma PAA and PAGN levels, and determining whether the dosage of a nitrogen scavenging drug needs to be adjusted based on whether the plasma PAA:PAGN ratio falls within a "target range," which was not numerically defined. (EX1009, 44-46.)

After issuing a Restriction Requirement and Horizon electing claims reciting methods of treating UCDs with GPB, the Examiner rejected the claims as obvious over U.S. Patent Appl. Pub. No. 2012/0022157 (EX1021; "Scharschmidt") in view of McGuire et al. (EX1011). (EX1009, 95-98, 101-102, 601-07.) According to the Examiner, Scharschmidt discloses a method for treating a nitrogen retention disorder comprising administering a PAA prodrug and measuring urinary PAGN levels, but not measuring PAA or PAGN levels in plasma or calculating a plasma PAA:PAGN ratio. (*Id.*, 602-03.) The Examiner also asserted that McGuire discloses measuring plasma PAA and PAGN after administering a PAA prodrug, and teaches that urinary testing is not as complete and thorough as plasma testing. (*Id.*, 603.) According to the Examiner, it would have been *prima facie* obvious to a POSA to modify Scharschmidt's method to measure plasma PAA and PAGN

levels instead of urinary PAA and PAGN, comparing them as a ratio, and evaluating any need to adjust dosage. (*Id.*)

In response, Horizon argued that McGuire describes a statistical approach to assess bioequivalency of two different PAA prodrugs, but 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 [sic] glyceryl tri-[4-phenylbutyrate] (GPB) is of utility in assessing the effectiveness of PAA to PAGN conversion." (*Id.*, 639-40.) Horizon further alleged that the claimed methods were "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." (*Id.*, 640.) Horizon further asserted:

> 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]).

(*Id.*, 640.) And Horizon incorrectly alleged that the prior art "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."[10] (*Id.*, 640-41.)

Not persuaded, the Examiner issued a Final Rejection, maintaining the rejection over Scharschmidt in view of McGuire. (*Id.*, 1261.) The Examiner asserted that McGuire reports two studies: (1) a bioequivalence study of GPB and NaPBA; and (2) a study of only GPB in 32 subjects. (*Id.*, 1268.) The Examiner stated that in the second study, PAA and PAGN levels were collected, "which values are easily compared as a ratio" and that "[w]hile it is acknowledged that the cited references do not explicitly disclose that [GPB] 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." (*Id.*, 1269.)

Horizon amended the claims in response to add a specific numerical target range of "1 to 2:5." (*Id.*, 1283-84.) Horizon also incorrectly alleged that "[t]he skilled artisan would expect that higher levels of the active metabolite (PAA)

[10] As discussed herein, the prior art, in fact, taught such methods. (*See*, *e.g.*, EX1010, S67 ("Dose optimization is required to maximize nitrogen removal, while minimizing the risk of toxicity, especially due to PA[A].").)

would lead to a proportionately higher response (as measured by PAGN levels) and increased nitrogen waste removal." (*Id.*, 1286.) But, given that the PAA to PAGN was known to be saturable, a POSA would have expected that higher levels of PAA would lead to a proportionately higher response (as measured by PAGN levels) and increased nitrogen waste removal only to the point of saturation, at which point higher levels of PAA would have no effect on PAGN formation. (EX1002, ¶33.)

Horizon further incorrectly argued that "[t]he 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."[11] (EX1009, 1286.)

As to the upper end of the claimed ratio, Horizon argued that "a patient whose PAA:PAGN ratio was greater than 2.5 at 12 hours post-dosing has a 36.4% chance of exceeding 400 μg/mL in plasma PAA sometime during the 24 hour period." (*Id.*, 1286-87.) Horizon then incorrectly alleged that using the plasma PAA:PAGN ratio was not taught in the prior art:

> 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

[11] Given that saturability was known, the use of the ratio was neither surprising nor unexpected. (*Id.*, ¶75; *see also* Section VI.B.1.)

> that the active moiety is not being effectively utilized, and increase the prodrug dosage may actually be deleterious, resulting in accumulation of PAA and associated toxicity.

(*Id.*, 1287.) Yet, this was already taught in the art. For example, MacArthur teaches dose optimization "to lessen the risk of attaining inappropriately high plasma phenylacetate levels, while maximizing its conversion to PAG[N]" (EX1010, S72; EX1002, ¶34), and specifically teaches that "[d]ose optimization will require both plasma and urine measurement of the metabolites, and phenylacetate and benzoate." (EX1010, S73; EX1002, ¶34.) Additionally, Thibault and Carducci both teach toxic amounts of PAA and the saturability of PAA-to-PAGN conversion that would have informed a POSA's understanding of the safe dosing of PAA-prodrugs, like GPB. (EX1006, 1693; EX1007, 3051-52, Figure 2; EX1002, ¶¶30-31.)

Horizon also asserted that Scharschmidt teaches away from using plasma metabolite levels, as it focuses on using urinary PAGN levels to adjust drug dosage, and that nothing in McGuire suggests utilizing plasma PAA:PAGN ratios for therapeutic purposes. (EX1009, 1288.)

In an Advisory Action, the Examiner rejected Horizon's response to the Final Office Action, because it included claim amendments that were unsupported by the specification for reciting a "target range [of] 1 to 2:5," required a new search, and did not put the application in condition for allowance. (*Id.*, 1296-97.)

In response, Horizon noted that the claim amendment seeking to add the range of "1 to 2:5" contained a typographical error, and stated that the numerical limitation should have read "1 to 2.5." (*Id.*, 1305.)

After an interview, the Examiner entered claim amendments to correct the typographical error and issued another Advisory Action that indicated that the claimed steps of "calculating" and "determining" are not given patentable weight under *Mayo Collaborative Services v. Prometheus Labs. Inc.*, 566 U.S. 66 (2012). (EX1009, 1311-13.) And the Examiner maintained the obviousness rejection. (*Id.*, 1313.)

Horizon responded by filing a Request for Continued Examination, cancelling all claims and adding claims reciting methods of treating UCDs in patients comprising administering a first dose that results in a plasma PAA:PAGN ratio less than 1 or greater than 2 or 2.5, then administering a second dose that is less than the first dose. (*Id.*, 1326-27.)

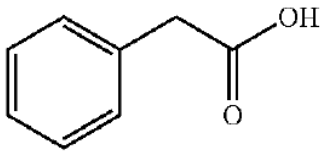
The Examiner then issued a Notice of Allowability, cancelled all but two claims and wholly rewrote those claims "to overcome potential issues under 35 U.S.C. 112," such that the claims were identical to now-issued claims 1 and 2. (*Id.*, 1337-40.)

V. CLAIM CONSTRUCTION

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretations ("BRI") in light of the specification of the '197 patent. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144-46 (2016).[12] Terms not explicitly discussed below are plain on their face and should be construed to have their plain and ordinary meanings. *See Chef America, Inc. v. Lamb-Weston, Inc*., 358 F.3d 1371, 1373 (Fed. Cir. 2004).

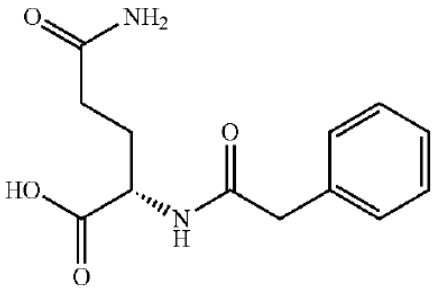
The parties have agreed to the construction of the following claim terms in federal district court litigation involving the '197 patent:

- "PAA" means "phenylacetic acid" or the structure shown below:



[12] To the extent the Office implements rules to construe the challenged claims in accordance with the principles of *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), Par submits that the same constructions provided herein will apply.

- "PAGN" means "phenylacetylglutamine" or the structure shown below:



- "a subject having a plasma PAA to PAGN ratio outside the target range of 1 to 2" means "a subject with a urea cycle disorder who has previously been administered a PAA prodrug and whose measured plasma PAA:PAGN ratio is outside the target range, i.e., either less than 1:1 or greater than 2:1";

- "a subject having a plasma PAA to PAGN ratio outside the target range of 1 to 2.5" means "a subject with a urea cycle disorder who has previously been administered a PAA prodrug and whose measured plasma PAA:PAGN ratio is outside the target range, i.e., either less than 1:1 or greater than 2.5:1."

A. The Preambles

Based on Horizon's position in federal district court litigation involving the '197 patent and in *Lupin, Ltd. v. Horizon Therapeutics, LLC*, IPR2018-00459 ("the Lupin IPR"), Horizon may argue that the preambles of claims 1 and 2 reciting "[a] method of treating a urea cycle disorder in a subject" should be construed to mean "[a] method of seeking ammonia control while minimizing the risk of PAA toxicity in a subject with a UCD." Horizon's proposed construction, however, does not comport with the BRI of the preambles in light of the specification. Indeed, a comparison of the claims to Horizon's proposed construction shows that

Horizon actually proposes construction of only one word in the preambles: "treating," which it seeks to have construed to mean "seeking ammonia control while minimizing the risk of PAA toxicity." The impropriety of Horizon's construction of "treating" is evidenced by the specification, which describes the term "treating" as follows:

> 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.

(EX1001, 20:22-37 (paragraph break added).)

The above description of the term "treating" does not constitute an "expression of manifest exclusion or restriction" or "clear disavowal of claim scope" that would warrant construing the term to have anything other than its plain and ordinary meaning. Instead, it uses language that merely "reinforces rather than undermines the ordinary descriptive meaning" of the term. *See Bayer CropScience*

AG v. Dow AgroSciences LLC, 728 F.3d 1324, 1329 (Fed. Cir. 2013). Indeed, this passage does not recite Horizon's limitations of "seeking ammonia control" and "minimizing the risk of PAA toxicity." In fact, the passage does not contain the words "ammonia," "control," or "toxicity" at all.

Additionally, to the extent that Horizon should instead contend that its proposed construction is based on some portion of the patent specification other than the above-quoted definition (for example, a particular embodiment), that contention would rely on improper importation of limitations from the specification that would unduly narrow the meaning of the word "treating." *See Wenger Mfg., Inc. v. Coating Mach. Sys., Inc.*, 239 F.3d 1225, 1237 (Fed. Cir. 2001) ("[I]t is improper to read limitations from the written description into a claim."). *See also Comark Commc'ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187 (Fed. Cir. 1998) (quoting *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1571 (Fed. Cir. 1988)) ("Although the specification may aid the court in interpreting the meaning of disputed claim language, particular embodiments and examples appearing in the specification will not generally be read into the claims."). In either case, Horizon's proposed construction deviates from the plain and ordinary meaning of the term "treating" and is without support from the specification.

The prosecution history similarly lacks any expression of manifest exclusion or restriction that would reflect a "clear disavowal of claim scope" with respect to the preambles or the term "treating." For example, at no point during prosecution of the '197 patent did the applicants "clearly and unmistakably rel[y]" on the preambles "to distinguish prior art." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002). Instead, the prosecution history shows that the inventors believed the allegedly inventive aspect of the claimed methods is the recited "target range" for plasma PAA:PAGN ratios, which has nothing to do with the particular disorder the claimed methods are intended to treat. For example, in responding to the Examiner's rejection, the applicants stated that "[t]he present claims are based on the unexpected observation that the plasma PAA:PAGN ratio provides an accurate measure of PAA prodrug metabolism." (EX1009, 1286.) The applicants went on to discuss plasma PAA:PAGN ratios extensively, making no mention of "treating a urea cycle disorder" as a basis for distinguishing over the prior art. (*Id.*, 1286-89.) Thus, there is no evidence in the prosecution history of any "expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope" with respect to the preambles. *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1326 (Fed. Cir. 2002).

Horizon's proposed construction should be rejected for at least the reasons discussed above, and the preambles should be given their as-written, plain and ordinary meaning: "[a] method of treating a urea cycle disorder in a subject."

B. "a plasma PAA to PAGN ratio within the target range of 1 to 2" and "a plasma PAA to PAGN ratio within the target range of 1 to 2.5"

Based on Horizon's position in the related litigation involving the '197 patent and the Lupin IPR, Horizon may argue that the phrase "administering . . . 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 [or 1 to 2.5]" should be construed to mean

> administering . . . a dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) effective to achieve a plasma PAA to PAGN ratio within the target range of [claim 1: 1 to 2] [claim 2: 1 to 2.5], wherein said effective dosage is determined by comparison of the plasma PAA to PAGN ratio to the target range, and wherein said effective dosage is increased if the plasma PAA to PAGN ratio is below the target range, and decreased if the plasma PAA to PAGN ratio is above the target range.

Horizon's proposed construction is comprised of the as-written claim phrase, plus two "wherein" clauses that add 51 additional words to the claim: (1) "wherein said effective dosage is determined by comparison of the plasma PAA to PAGN ratio to the target range"; and (2) "wherein said effective dosage is increased if the plasma PAA to PAGN ratio is below the target range, and decreased if the plasma PAA to PAGN ratio is above the target range." These "wherein" clauses are

positive claim limitations because they provide elements that are necessary—in Horizon's view, at least—to define the claimed method: (1) the specific manner in which an "effective" dosage is determined; and (2) how to determine whether to increase or decrease that dosage.

Because they are imported from the specification, it is improper to read these limitations into the claims. *See Wenger Mfg.*, 239 F.3d at 1237; *Electro Med. Sys., S.A. v. Cooper Life Scis., Inc.*, 34 F.3d 1048, 1054 (Fed. Cir. 1994) ("When the meaning of words in a claim is in dispute, the specification . . . can provide relevant information about the scope and meaning of a claim. However, claims are not to be interpreted by adding limitations appearing only in the specification."). For example, the specification recites methods wherein "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." (EX1001, 19:14-17.) The specification further recites methods for "adjusting the dosage of a PAA prodrug in a subject," wherein the method comprises "determining whether to adjust the dosage of the PAA prodrug" and wherein "a PAA:PAGN ratio of less than 1 indicates the PAA prodrug dosage needs to be adjusted upwards, while a plasma PAA:PAGN ratio above 2.5 indicates that the PAA prodrug dosage needs to be adjusted downwards." (*Id.*, 16:18-31.) Taking these disclosures from the specification and attempting to

import them as claim limitations is improper. *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001) (describing the importation of limitations from the specification into the claims as "one of the cardinal sins of patent law").

Further, the as-written claim phrase simply recites "administering . . . a dosage" of GPB "effective to achieve a plasma PAA to PAGN ratio" within a certain "target range." The plain language of this claim phrase, therefore, does not implicate methods of determining an effective dosage, nor does it discuss dose adjustment.

Additionally, Horizon's proposed construction would render the '197 patent claims indefinite. *See*, *e.g.*, *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373 (Fed. Cir. 2003); 1 Ann. Pat. Digest § 7.41 ("Claim constructions that will result in an indefinite claim should be avoided."). Indeed, Horizon's two "wherein" clauses both recite the term "said effective dosage," but there is no antecedent basis in the '197 patent claims for that term.

To the extent the Board believes this claim phrase needs construction Par proposes that a POSA would understand that the BRI of this phrase to mean "administering a dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) effective to achieve a plasma PAA:PAGN ratio in plasma that is no less than 1:1 and no greater than 2:1" (claim 1) or "administering a dosage of glyceryl tri-[4-phenylbutyrate]

(HPN-100) effective to achieve a plasma PAA:PAGN ratio in plasma that is no less than 1:1 and no greater than 2.5:1" (claim 2). (EX1002, ¶43.) This construction simply clarifies that the recited "target range" refers to a range of plasma PAA:PAGN ratios, with the range having a lower bound of 1:1 and an upper bound of 2:1 or 2.5:1. (*Id.*)

VI. IDENTIFICATION OF THE CHALLENGE (37 C.F.R. § 42.104(b))

Par requests IPR of claims 1 and 2 of the '197 patent on the grounds of unpatentability listed in the table below. Per 37 C.F.R. § 42.6(c), copies of the cited prior art references accompany the Petition. In support of the proposed Ground for unpatentability, this Petition is also accompanied by the declaration of Dr. Sondheimer (EX1002), an internationally-renowned expert in the genetic causes, diagnosis, and treatment of UCDs.

Ground	35 U.S.C. Section (pre-3/16/2013)	Claims	Index of References
1	103(a)	1 and 2	Lee (EX1004), Praphanphoj (EX1005), Thibault (EX1006), and Carducci (EX1007)

This Ground establishes a reasonable likelihood that each of the '197 patent claims are unpatentable. This Ground is also not the same or substantially the same as art and arguments raised during prosecution. And while Lee, Praphanphoj, Thibault, and Carducci were cited in an Information Disclosure Statement ("IDS") submitted during prosecution (EX1009, 110, 674, 680), the

Examiner did not reject the claims in view of these references, and Horizon did not highlight these references for the Examiner. Therefore, the Board should not exercise its discretion under § 325(d) to deny institution of this Petition. *See*, *e.g.*, *Limelight Networks, Inc. v. Mass. Inst. of Tech.*, IPR2017-00249, Paper 9 at 7 (PTAB May 18, 2017) ("We are not persuaded . . . that a citation to prior art in an IDS, without substantive discussion of the reference by the Examiner, is sufficient reason to exercise our discretion under 35 U.S.C. § 325(d).").

A. Ground 1: Claims 1 and 2 Would Have Been Obvious Over Lee, Praphanphoj, Thibault, and Carducci.

As supported by the declaration of Dr. Sondheimer, a POSA would have had reason and the know-how to arrive at claims 1 and 2 in view of Lee, Praphanphoj, Thibault, and Carducci with a reasonable expectation of success. (EX1002, ¶¶50-71.) Each of Lee, Praphanphoj, Thibault, and Carducci are directed to methods of administering PAA or PAA-prodrugs to patients. (*Id.*, ¶51.) As discussed below, a POSA would have had a reason and the know-how to modify Lee's method of dosing GPB, as informed by Praphanphoj, Thibault, and Carducci, and would have been able to do so successfully. (*Id.*, ¶¶50-71.)

1. Administering GPB to Treat UCD Patients Was Well-Known In the Art.

Lee discloses that GPB was preferable over the standard UCD treatment with NaPBA because (1) GPB provides the same amount of active ingredient in a

smaller dose (four teaspoonfuls instead of forty tablets), (2) decreases the amount of sodium intake for patients, (3) avoids the unpleasant taste of NaPBA, (4) and provides PAA at a more constant level. (EX1004, 222, 224, 226-27; *see also* EX1020, ¶65; EX1023, 3:48-55; EX1002, ¶53.) As such, a POSA reading Lee would have had a reason to use GPB in place of prior art PAA-prodrugs that had undesirable properties. (EX1002, ¶54.) And as discussed in Sections IV.B.3.-IV.B.4. and below, a POSA would have had a reason to look to art related to PAA's metabolism, as GPB is a PAA-prodrug that converts to PAA upon its administration. (EX1020, ¶23; EX1023, 4:66-5:2; EX1004, 222, 224; EX1002, ¶54.)

2. A POSA Would Have Had a Reason to Determine a Subject's PAA:PAGN Ratio.

A POSA reading Lee would have been motivated to look to Praphanphoj, Thibault, and Carducci to determine a therapeutic window for safe and effective GPB-based treatment in a subject with a UCD by using the subject's plasma PAA:PAGN ratio. (EX1002, ¶¶27-37, 55.) Indeed, Praphanphoj, Thibault, and Carducci each provides useful data on the plasma levels of PAA and PAGN during treatment and data concerning toxicity, from which a POSA reading Lee could determine a safe and effective course of treatment with GPB. (*Id.*, ¶55.)

First, Carducci teaches that the body's conversion of PAA to PAGN was a saturable process, with PAGN plasma levels plateauing at ~320 μg/mL. (EX1007,

3052, Figure 2; EX1002, ¶56.) As such, a POSA would have known that around the point of saturation PAA plasma levels would begin to build up and not result in a steady conversion into PAGN. (EX1002, ¶56.)

Second, a POSA would have known that PAA plasma levels in excess of 906 µg/mL resulted in PAA-induced neurotoxicity, as taught in Thibault and Praphanphoj. (EX1006, 1693; EX1005, Summary, Table 1; EX1002, ¶57.) And in fact, Praphanphoj reported that this toxicity was fatal in at least two UCD patients. (EX1005, Summary; EX1002, ¶57.)

Third, a POSA taking the data from these references in combination would have easily understood that doses providing plasma PAA:PAGN values exceeding 906/320 µg/mL (a ratio of 2.8) would lead to toxicity with no benefit to the patient through increased conversion of PAA to PAGN.[13] (EX1002, ¶57.)

Thus, a POSA would have been able to determine the high end of PAA's therapeutic window, i.e., the minimum effective concentration for adverse

[13] A POSA's understanding that this ratio would result in toxicity would be further confirmed by the fact that intravenous dosing of 250 mg/kg PAA was shown to be safe and effective (EX1015, 14), which is lower than Thibault's intravenous doses of 266 mg/kg and 374 mg/kg PAA that were shown to be toxic (EX1006, Table 2 (Dose levels 3 and 4), 1693; EX1002, ¶57 n.6).

responses. (*Id.*, ¶36-37, 57.) Indeed, in doing so, a POSA would have been aware that determining the dose at which any further increases in the dose would produce adverse responses would have been important for safely using a drug. (EX1012, 19-20; EX1002, ¶¶58-59.) Here, in the case of GPB, that would be the saturation point of PAA-to-PAGN conversion and resultant PAA-induced toxicity. (EX1002, ¶58.)

Moreover, because one of the benefits of GPB is that it "exhibits slow release characteristics" (EX1004, 222), the continuous infusion studies of Thibault and Carducci would have provided a POSA excellent guidance for the pharmacokinetics of GPB. (EX1002, ¶59.) Indeed, as Dr. Sondheimer discusses, continuous infusion studies provide the best guidance on determining PAA's potential toxicity because such studies provide the most accurate estimation of plasma concentration for a drug that is chronically administrated. (EX1012, 17; EX1002, ¶59.) Therefore, both Thibault and Carducci would have provided important information about the correlation between drug dose and the resultant PAA plasma levels and PAGN plasma levels. (EX1002, ¶59.)

Additionally, contrary to Horizon's position in the Lupin IPR, a POSA would not have disregarded Thibault's and Carducci's disclosures because the reported studies were done in cancer patients. (*Id.*, ¶60.) The symptoms of toxicity reported in Thibault and Carducci are similar to the description of PAA-

dependent toxicity reported in the Buphenyl label and Ammonul label, i.e., drugs for treating UCDs, based on studies in cancer patients. (EX1006, 1693; EX1007, 3051; EX1014, 4; EX1015, 8; EX1002, ¶60.) Similarly, Praphanphoj reports these same features of PAA-dependent toxicity, e.g., "letharg[y]," "irritability," "unresponsive [state]," and "somnolen[ce]" were found in UCD patients who received fatal overdoses of PAA. (EX1005, 131-133; EX1002, ¶60.) A POSA, therefore, would expect toxicity concerns in cancer patients and UCD patients to be the same. (EX1002, ¶60.)

Upon determining the high end of GPB's therapeutic window, a POSA would have had a reason to determine the low end. (EX1012, 18-20; EX1002, ¶61.) Along those lines, a POSA reading Lee would have determined that evaluating PAA and PAGN plasma levels would inform the need for dosage increases due to low plasma PAA:PAGN ratios. (EX1002, ¶61.) Indeed, Lee recognized that eight out of ten patients in Lee's study received lower-than-recommended doses of PBA. (EX1004, 226; EX1002, ¶61.) Lee stated that this patient population did not experience optimal ammonia control, noting that "[i]ncreasing dose in these subjects to within the labeled range (BUPHENYL package insert) might improve ammonia control and, considering the high proportion of UCD patients with self-reported neurological disability, potentially improve neurological outcome." (EX1004, 226; EX1002, ¶61.) Lee reports that

for these subjects the mean time-normalized area under the curve ("TN-AUC") of PAA was 596 μg*h/mL and of PAGN was 1133 μg*h/mL, yielding a plasma PAA:PAGN ratio of 0.52. (EX1004, Table 3; EX1002, ¶61.) Notably, Lee selected the dose of GPB for these subjects to be "equivalent" to the PBA dose the subject was receiving. (EX1002, 222; EX1002, ¶61.) As such, the eight patients receiving a lower-than-recommended dose of PBA would have similarly received a lower-than-recommended dose of GPB. (EX1002, ¶61.) A POSA would have understood from Lee, consequently, that patients with plasma PAA:PAGN ratios around 0.52 would require a dosage adjustment (increased dose) in order to increase the plasma PAA:PAGN ratio such that the desired therapeutic response to GPB was achieved. (EX1002, ¶61.)

With that in mind, a POSA would have looked to other studies—such as Thibault and Carducci—in which PAA levels achieved effectiveness without causing toxicity, because PAA was known to be neurotoxic and its conversion to PAGN was known to be saturable. (EX1006, 1692-93; EX1007, Figure 2, 3052; *see also* EX1010, S72; EX1002, ¶¶27-35, 56-61.) In particular, Praphanphoj discloses that a patient properly treated with PAA using a bolus dose followed by a continuous infusion had an initial plasma PAA:PAGN ratio of 4.5 that decreased to 1.7, with the initial elevation of plasma PAA:PAGN ratio due to the slow onset of

PAA's conversion to PAGN.[14] (EX1005, Table 1; EX1002, ¶63.) As such, a POSA would have known that plasma PAA:PAGN ratios around 1.7 would have been both safe and effective. (EX1002, ¶63.)

Further, a POSA would have had a reason to measure and take into consideration a patient's plasma PAA:PAGN ratio when developing a method of dosing GPB in view of the prior art. (EX1002, ¶64.) First, as discussed above Lee, Praphanphoj, Thibault, and Carducci in combination disclose safe and effective ranges for PAA in the plasma, as well as the point at which PAA's effectiveness plateaus and becomes toxic due to saturation in its conversion to PAGN. (EX1004, Table 3, 226; EX1005, Summary, 130-133, Table 1; EX1006, 1693; EX1007, Figure 2; EX1002, ¶64.) And a POSA would have considered this information when designing a dosing regimen, as taught and suggested in the prior art to avoid toxicity and maximize efficacy. (*See* Sections IV.B.4.; EX1002, ¶64.)

[14] Praphanphoj reports (1) a PAA plasma level of 3.5 mmol/L (476 µg/mL) and a PAGN plasma level of 0.4 mmol/L (105.6 µg/mL), i.e., a PAA:PAGN ratio of 4.5, at 17 hours post-infusion; and (2) a PAA plasma level of 1.5 mmol/L (204 µg/mL) and a PAGN plasma level of 0.45 mmol/L (118.8 µg/mL), i.e., a PAA:PAGN ratio of 1.7 at 32 hours post-infusion. (EX1005, Table 1; EX1002, ¶63 n.7.)

That a prior art reference does not expressly calculate a "PAA:PAGN ratio" would not have negated the prior arts' teachings with respect to dosing and would, nonetheless, have guided a POSA to measuring a patient's plasma PAA:PAGN ratio. (EX1002, ¶62.) *See also WesternGeco LLC v. ION Geophysical Corp.*, 889 F.3d 1308, 1326-27 (Fed. Cir. 2018) (affirming the Board's finding in an IPR that claims were obvious where a prior art reference disclosed all of the method steps except for accounting for a "feathering angle" and the petitioner's expert testified that a POSA knew how to compensate for feathering angles).

In fact, as discussed above, a POSA would have already had a reason to use the plasma PAA:PAGN ratio to determine the high end of GPB's therapeutic window based on the teachings of Thibault, Praphanphoj, and Carducci with respect to toxicity and PAA-to-PAGN conversion's saturability. (EX1002, ¶62.) Further, a POSA would have understood from Lee's teachings regarding underdosing that the low end of GPB's therapeutic window includes the plasma levels of PAA and PAGN reported in Lee. (*Id.*) The prior art combined with a POSA's knowledge, therefore, would have directed a POSA to arrive at the claimed invention. *KSR*, 550 U.S. at 418 (stating that an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.").

3. A POSA Would Have Had a Reason to Determine if a Subject's Plasma PAA:PAGN Ratio Was Outside a Target Range of 1 to 2 or 2.5 and Adjust the Dose of GPB Accordingly.

Viewing Lee, Praphanphoj, Thibault, and Carducci together, a POSA would have known that GPB dosages that result in a plasma PAA:PAGN ratio around 0.52 are ineffective and signal a need to increase the dose of medication. (EX1004, Table 3, 226; EX1005, Table 1 (disclosing PAA and PAGN levels in an effectively treated patient); EX1002, ¶65.) This is because the plasma levels of PAA (the active metabolite of GPB) need to be sufficiently high to be available for conjugation with glutamine and thereby provide efficacy. (EX1002, ¶65.)

Indeed, Lee teaches that patients with a mean plasma PAA:PAGN ratio of 0.52 did not achieve sufficient ammonia control (EX1004, Table 1, 226; EX1002, ¶65), while Praphanphoj teaches an effectively treated patient had a plasma PAA:PAGN ratio of 1.7 (EX1005, Table 1; EX1002, ¶65). Thus, a POSA would have recognized that an effective dose of GPB is one that achieves plasma PAA:PAGN ratios around 1.7 or higher. POSAs would have also understood that there are ratios even lower than 1.7, but not as low as 0.52, where the corresponding dose of GPB is not effective. (EX1002, ¶65.) Further, a POSA would have known that dosages that result in a plasma PAA:PAGN ratio at or above the high end of the therapeutic window can cause undesirable PAA-dependent toxicity, i.e., plasma PAA:PAGN ratios around 2.8 and higher.

Thibault, Praphanphoj, and Carducci teach as much. (EX1005, Summary, Table 1; EX1006, 1692-93; EX1007, Figure 2, 3052; *see also* Section VI.A.2.; EX1002, ¶66.) A POSA, therefore, would have known that a dosage of GPB that achieves plasma PAA:PAGN ratios of at least 1.7 would be effective and that such dosages should be adjusted to avoid plasma PAA:PAGN ratio levels of about 2.8 and higher in order to avoid PAA-induced toxicity. (EX1002, ¶67.)

As such, the prior art teaches safely treating a UCD patient by administering a dose of GPB to achieve plasma PAA:PAGN ratios that are within the range of about 1.7 to about 2.8. As such, the claimed ranges of plasma PAA:PAGN ratios of 1 to 2 (claim 1) and 1 to 2.5 (claim 2) overlap the range of safe and effective plasma PAA:PAGN ratios—as well as each other element of the claims—are disclosed in the prior art; rendering the claimed ranges *prima facie* obvious. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003); *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004).

This presumption of obviousness can only be rebutted by a showing that (1) "the prior art taught away from the claimed invention" or (2) "there are new and unexpected results relative to the prior art." *Iron Grip*, 392 F.3d at 1322 (citations omitted). As discussed in Sections VI.B.1. and Sections VI.B.5., the claimed invention does not achieve any unexpected results and no teaching away from the claimed plasma PAA:PAGN ratios exits. Accordingly, Horizon cannot

rebut the presumption that the claimed plasma PAA:PAGN ratio ranges are obvious.

4. A POSA Would Have Had a Reasonable Expectation of Successfully Practicing the Claimed Methods.

A POSA would have had a reasonable expectation of successfully practicing a method of treating a subject with a UCD by determining the subject's plasma PAA:PAGN ratio and administering an adjusted dose of GPB based on that ratio that results in a plasma PAA:PAGN ratio within a target range of 1 to 2 (claim 1) or 2.5 (claim 2). (EX1002, ¶68.) This is because, in part, Lee, Praphanphoj, Thibault, and Carducci provide data from which a POSA could have readily determined methods of administering GPB that are safe and effective, such that PAA's conversion to PAGN would not be saturated—thereby resulting in undesirable PAA toxicity. (EX1002, ¶¶55-67, 69.) In fact, the Ammonul label cited to Thibault to provide safety information. (EX1015, 8; EX1002, ¶29.) Further, applying Praphanphoj's, Thibault's, and Carducci's known techniques of measuring PAA and PAGN levels to Lee's known method of using GPB to treat UCDs would have achieved predictable results because the combination of references would have allowed a POSA to establish the therapeutic window for GPB administration. (EX1012, 18-20; EX1002, ¶69.)

And because the conversion of PAA to PAGN was known to be a saturable process, the ratio between PAA and PAGN required to reach an effective and safe

PAA dosage amount would have been well-known and the useful therapeutic window for GPB was well-understood. (EX1002, ¶70.) Indeed, both Carducci and Thibault disclosed the kinetics of PAA's conversion to PAGN, from which a POSA could have established proper GPB dosing. (EX1006, 1692-93; EX1007, 3052, Figure 2; EX1002, ¶70.) Thus, claims 1 and 2 would have been obvious. *KSR*, 550 U.S. at 416.

Moreover, a POSA could have easily optimized GPB's dosing to be within its therapeutic window, such that the treatment was safe and effective—namely, achieving a plasma PAA:PAGN ratio within a target range of 1 to 2 (claim 1) or 2.5 (claim 2). (EX1002, ¶71.) For instance, as discussed above, a POSA would have determined from Carducci and Thibault that a plasma PAA:PAGN ratio of less than about 2.8 would avoid toxicity. And a POSA would have determined from Lee and Praphanphoj that a plasma PAA:PAGN ratio of 1.7 and higher would be effective. (*See* Section VI.A.3; *see also* EX1002, ¶¶56-67, 61-63, 71.) As such, a POSA would have been motivated to adjust the GPB dosage to achieve optimized ratios that are less than about 2.8—which includes ratios that are less than 2 (claim 1) and ratios that are less than 2.5 (claim 2). (EX1002, ¶71.) Similarly, to effectively treat UCD patients, a POSA would have been motivated to adjust the GPB dosage to achieve optimized ratios of around 1.7 and higher—which includes ratios that are greater than 1 (claims 1 and 2). Indeed, a subject's

plasma PAA:PAGN ratio would have been a result-effective variable based on (1) the amount GPB administered to the patient and (2) the patient's inherent metabolic conversion of GPB into PAA and PAGN that would have affected the safety and efficacy of the GPB dose given. (*Id.*, ¶71.)

To that end, the '197 patent claims simply recite dose optimization suggested in the prior art. (*Id.*, ¶71.) However, where the "general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation," which is all the '197 patent claims do. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012). *See also Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1379 (Fed. Cir. 2008) (discovery of an optimal value in a known process is usually obvious).

B. Objective Indicia of Nonobviousness Do Not Weigh In Favor of Patentability of Claims 1 and 2.

In addition to Par's strong showing of *prima facie* obviousness, objective indicia must be taken into account, although it does not control the obviousness conclusion. *See Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988); *Leo Pharm. Prods. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (finding that before the Board consideration of objective indicia is part of the whole obviousness analysis, not just an afterthought). Where a strong showing of *prima facie* obviousness exists, however, the Federal Circuit has repeatedly held that even relevant objective indicia supported by substantial evidence is still

insufficient to overcome obviousness. *See*, *e.g.*, *Leapfrog Enterprises Inc. v. Fisher-Price Inc.,* 485 F.3d 1157, 1162 (Fed. Cir. 2007).

Objective evidence must be attributable to the claimed invention, and apart from what is unclaimed or in the prior art. *See In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011); *see also Gnosis S.p.A. v. Merck & Cie*, IPR2013-00117, Paper 71, at 35 (PTAB June 20, 2014) ("Based on evidence before us, we are not persuaded that 'the objective indicia of non-obviousness [is] tied to the novel elements of the claim at issue' in this case . . . As such, insufficient nexus exists."); *Medtronic, Inc. v. Marital Deduction Trust*, IPR2014-00100, Paper 46, at 28 (PTAB Mar. 24, 2015) ("[N]o evidence of record indicates that a nexus exists between the sales of the mentioned devices and novel or non-obvious aspects of the subject matter recited in the challenged claims.").

Horizon may argue that objective indicia of unexpected results, long-felt but unmet need, failure of others, teaching away, or commercial success exist. Further, Par requests an opportunity to rebut any evidence of objective indicia upon which Horizon may rely. *See*, *e.g.*, *Amneal Pharms., LLC v. Supernus Pharms., Inc.*, IPR2013-00368, Paper 8, at 12-13 (PTAB Dec. 17, 2013).

1. No Unexpected Superior Results.

During prosecution, Horizon argued that "[t]he 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."[15] (EX1009, 223.) But, as discussed above, PAA-to-PAGN conversion's saturability and PAA-dependent toxicity were known in the prior art and a POSA would have known that monitoring a patient's plasma PAA:PAGN ratio based on these issues would have been useful, and even generally recommended in the medical field. (*See* Sections IV.B.3.-IV.B.4.; EX1002, ¶75.) Arriving at the claimed ratios, therefore, was neither surprising nor unexpected. (EX1002, ¶75.) Thus, any argument that the claimed ratio was unexpected cannot be attributed to anything not found in the prior art. (*Id.*) *Kao*, 639 F.3d at 1068; *Gnosis*, IPR2013-00117, Paper 71 at 35.

Moreover, any argument that a more optimized dose could be obtained by using the specific claimed ratios, even if true, would represent merely a difference in degree of treatment, not a difference in kind, which is insufficient to change the obviousness calculus here. *See*, *e.g.*, *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) ("Unexpected results that are probative of nonobviousness are those that are 'different in kind and not merely in degree from the results of the prior art.'").

[15] Horizon has reiterated this argument in the Lupin IPR. *See* Lupin IPR, Paper 7 at 54-55.

2. No Long-Felt Need or Failure of Others.

A showing of a long-felt and unmet need requires that the need must have been a persistent one that was recognized by those of ordinary skill in the art. *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332-33 (Fed. Cir. 2009). The long-felt need must not have been satisfied by another before the invention. *Newell Companies v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). The invention must in fact satisfy the long-felt need. *Media Techs. Licensing, LLC v. Upper Deck Co.*, 596 F.3d 1334, 1338-39 (Fed. Cir. 2010). Failure of others to find a solution to the problem which the patent purports to solve is also relevant in determining nonobviousness. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966).

Horizon has argued in the Lupin IPR that there existed a long-felt but unmet need for a biomarker for dose optimization that could be obtained at any point in the day from a UCD patient regardless of meal intake. *See* Lupin IPR, Paper 7 at 55-56. The various nitrogen scavenging drugs in the prior art, however, had long been safely and effectively used to treat UCDs well before April 20, 2012 without requiring a physician to measure a patient's plasma PAA:PAGN ratio. (EX1014; EX1015; EX1002, ¶77.) Indeed, the label for Horizon's commercial GPB product, Ravicti, does not include language instructing physicians to use the '197 patent's claimed methods (*see* Section VI.B.4.). Moreover, POSAs have been successfully

treating UCDs for many years without using the claimed method. (EX1002, ¶78.) Indeed, the possibility of toxicity is remote for those using PAA and PAA-prodrugs within dosing guidelines—which had already taken into account what was known with regard the therapeutic window for these drugs from references such as Thibault. (*Id.*; *see also* EX1015, 8; EX1014, 4.)

Thus, the claimed methods did not meet any long-felt need before April 20, 2012, and others did not fail at developing methods of treating subjects with known nitrogen scavenging drugs, such as GPB. (*Id.*, ¶¶77-79.)

3. No Commercial Success.

To the extent Horizon seeks to rely on any sales of Ravicti, Horizon's commercial GPB product, as showing purported commercial success, that attempt should be rejected. There is no nexus between the claimed subject matter and Ravicti. In fact, the FDA has rejected Horizon's efforts to add the claimed method to the Ravicti label. For example, in the drug approval package for Ravicti, the FDA stated: "There were limitations to the strength of evidence provided in the NDA to support inclusion of information proposed by the applicant in the product label on how to modify dose based on various biomarkers, aside from venous ammonia levels." (EX1016 at 6.) The FDA further stated:

> The Clinical Pharmacology and Clinical reviewers concurred that PAA and U-PAGN levels could be important in optimally managing an individual patient. The Clinical Pharmacology reviewer could not agree that

> a specific PAA/PAGN (plasma) ratio had been appropriately established that could serve as the "cut point" that should be applied to all patients to definitively guide dose adjustments.

(*Id.* at 18.) Thus, neither the claimed "target" plasma PAA:PAGN ratios, nor any other "target" plasma PAA:PAGN ratio, appears on the label. (*See generally* EX1013.)

To the extent Horizon claims a presumption of nexus exists due to Ravicti's label allegedly being coextensive with the '197 patent's claims, where (as here) a commercial product is covered by multiple patents, no presumption applies. *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1289, 1299 (Fed. Cir. 2010) ("This is not a situation where the success of a product can be attributed to a single patent, because Abbott's Exactech product embodied at least two patents: the [prior art] '382 patent and the [asserted] '551 patent."), *vacated for reh'g en banc on other grounds*, 374 F. App'x 35 (Fed. Cir. 2010), *reinstated in relevant part*, 649 F.3d 1276 (Fed. Cir. 2011) (en banc).

Horizon still has listed eight patents that recite methods of using GPB in the Orange Book for Ravicti. (EX1027.) And the Orange Book also lists a patent covering the GPB compound that issued almost 14 years before Ravicti came to market. (*Id.*) Thus, to establish that any alleged commercial success is attributable to the '197 patent, Horizon must present evidence showing that the commercial success is not attributable to subject matter claimed in any of these other patents.

Therasense, 593 F.3d at 1299 (commercial success not probative of the nonobviousness of a later patent when an earlier patent issued before the drug came to market); *see also J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) ("[T]he asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art.").

4. Alleged Copying By Generic Drug Makers Is Irrelevant.

Horizon may argue that Par and other generic drug companies seek to copy the invention of the '197 Patent by commercializing generic versions of GPB. Because copying "is required for FDA approval" of generic drugs, any "evidence of copying in the [generic drug] context is not probative of nonobviousness." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

5. No Teaching Away.

Petitioner is not aware of any teachings in the prior art that would teach away from the Ground presented in this petition that renders the '197 patent claims obvious.

VII. CONCLUSION

Each of claims 1 and 2 would have been obvious over the asserted prior art for the reasons stated in Section VI. Thus, the Board should institute IPR on the ground of invalidity presented in this Petition.

VIII. MANDATORY NOTICES (37 C.F.R. § 42.8)

Real Parties-In-Interest (37 C.F.R. § 42.8(b)(1)): Par is the real-party-in-interest for this proceeding. Out of an abundance of caution, and as a result of ongoing integration and reorganization activities, Petitioner identifies the following additional entities as actual or potential real-parties-in-interest who, going forward, may have control over this proceeding: Endo International PLC; Endo DAC; Endo Luxembourg Holding Company S.a.r.l.; Par Pharmaceutical Holdings, Inc.; Luxembourg Endo Specialty Pharmaceuticals Holding II S.a.r.l.; Luxembourg Endo Specialty Pharmaceuticals Holding I S.a.r.l.; and Par Pharmaceutical Companies, Inc. No other parties exercised or could have exercised control over this petition; no other parties funded or directed this petition. *See* Office Patent Trial Practice Guide, 77 Fed. Reg. 48759-60.

Related Matters (37 C.F.R. § 42.8(b)(2)):

Administrative: (1) *Lupin Ltd. v. Horizon Therapeutics, LLC*, IPR2018-00459 (terminated due to settlement).

Judicial: *Horizon Therapeutics, LLC v. Par Pharmaceutical, Inc.*, 17-cv-5901 (D.N.J.).

Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):

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Notice of Service Information (37 C.F.R. § 42.8(b)(4)): Please direct all correspondence to lead counsel and back-up counsel at the above address. Petitioner consents to email service at: dsilverstein@axinn.com, aburgy@axinn.com, cgallo@axinn.com, and Ravicti197-Axinn@axinn.com.

Procedural Statements: This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed are a Power of Attorney and Exhibit List under 37 C.F.R. § 42.10(b) and § 42.63(e), respectively. Petitioner submits the required fees with this Petition. The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Account No. 013050.

Word Count Certification (37 C.F.R. § 42.24(a)): Petitioner certifies that the foregoing complies with the type-volume limitation of 37 C.F.R. § 42.24 and contains 10,890 words based on the word count indicated by the word processing system used to prepare the paper, and excluding those portions exempted by § 42.24(a)(1).

Dated: August 16, 2018

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CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e); 42.105(a))

The undersigned hereby certifies that the above-captioned "Petition for *Inter Partes* Review of U.S. Patent No. 9,561,197 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123," including its supporting evidence (Exhibits 1001 – 1032), was served in its entirety on August 16, 2018 upon the following parties via FedEx®, a means at least as fast and reliable as Priority Mail Express®:

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