IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUPIN LTD. and LUPIN PHARMACEUTICALS INC.

Petitioners,

v.

HORIZON THERAPEUTICS, LLC

Patent Owner.

IPR2017-01160

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,326,966 PURSUANT TO §§ 35 U.S.C. 311-319 AND 37 C.F.R. § 42

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I. INTRODUCTION

Lupin Ltd. and Lupin Pharmaceuticals Inc. ("Petitioner" or "Lupin") petition for *Inter Partes* Review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42 of claims 1 to 15 of U.S. Patent No. 9,326,966 ("the '966 Patent," Ex. 1003).

The '966 Patent is directed to methods of administering and adjusting the dosage of the nitrogen scavenging drug glyceryl tri-[4-phenylbutyrate] (also known as glycerol phenylbutyrate and HPN-100) in patients with urea cycle disorders ("UCDs"), based on measurement of the fasting plasma ammonia level of a subject. Nitrogen scavenging drugs, and their use in reducing plasma ammonia levels in UCD patients, were well known long before the '966 Patent was filed.

The '966 Patent discloses a purportedly novel method of measuring a fasting plasma ammonia level of a subject who has received glyceryl tri-[4-phenyl-butyrate], comparing this fasting plasma ammonia level to an upper limit of normal ("**ULN**") for plasma ammonia level, and then adjusting the dosage of glyceryl tri-[4-phenyl-butyrate] if the measured fasting plasma ammonia level is between half of the ULN and the ULN for plasma ammonia level. Increasing the dose of nitrogen scavenging drugs to lower a subject's fasting plasma ammonia level and to maintain normal ammonia levels has been done for decades.

As shown below, the '966 Patent claims describe nothing more than conventional practice by physicians that was disclosed in the prior art cited herein

and known before September 30, 2011, the earliest possible priority date of the '966 Patent claims. Accordingly, IPR should be instituted and the claims should be cancelled.

II. SUMMARY OF '966 PATENT AND ITS PROSECUTION HISTORY

The '966 Patent was filed on December 3, 2015 as a continuation of U.S. Application No. 14/816,674, filed August 3, 2015, now Patent No. 9,254,278 (the "'278 Patent"), which is a continuation of U.S. Application No. 13/775,000, filed February 22, 2013, now Patent No. 9,095,559 (the "'559 Patent"), which is a continuation of U.S. Application No. 13/417,137, filed March 9, 2012, now Patent No. 8,404,215 (the "'215 Patent"). The '966 Patent claims the benefit of U.S. Provisional Application No. 61/564,668, filed November 29, 2011, and U.S. Provisional Application No. 61/542,100, filed September 30, 2011.

For purposes of this IPR only, Petitioner will assume that the '966 Patent claims are entitled to the earliest possible claimed priority date, which is the September 30, 2011 filing date of U.S. Provisional Application No. 61/542,100.

A. Independent Claims

Claims 1, 6, 9, and 12, the four independent claims of the '966 Patent, recite:

> 1. A method of treating a subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than

the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level,

wherein the upper limit of normal for plasma ammonia level is in the range of 26-64 μmol/L.

6. A method of treating a pediatric subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the pediatric subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

9. A method of treating an adult subject with a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and who has a fasting plasma ammonia level less

than the upper limit of normal for plasma ammonia level, the method comprising:

(a) measuring a fasting plasma ammonia level for the adult subject;

(b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and

(c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level.

12. A method of treating a patient having a urea cycle disorder comprising:

(a) administering an initial effective dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) to the patient, wherein the initial effective dosage is calculated based on body surface area of the patient;

(b) measuring the patient's urinary PAGN and/or fasting plasma ammonia level to determine whether to change the dosage of the glyceryl tri-[4-phenylbutyrate] (HPN-100); and

(c) administering a subsequent effective dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) to the patient that is either the same as the initial effective dosage or is an increased dosage, wherein said increased dosage, if any, is calculated based on the patient’s urinary PAGN and/or fasting plasma ammonia level.

(Ex. 1003 at 24:11–25; 24:38-50; 24:57-25:2; 25:9-26:6.)

B. Prosecution History

The prosecution of the ’966 Patent was brief, lasting five months from filing to patent issue. Patent Owner filed the application leading to the ’966 Patent on December 3, 2015. The Examiner issued a non-final rejection on February 5, 2016, rejecting all claims for nonstatutory double patenting over claims from the ’278 Patent, the ’215 Patent, the ’559 Patent, and U.S. Patent No. 8,642,012 (the “’012 Patent”). (Ex. 1025 at 118-125.) In response, the applicant canceled some claims, submitted additional claims, and submitted a terminal disclaimer over the four patents. (Ex. 1025 at 187-192.) The Examiner then issued a Notice of Allowance on March 8, 2016. (Ex. 1025 at 204.)

III. BACKGROUND ON THE UREA CYCLE, UCDs, AND NITROGEN SCAVENGING DRUGS

The urea cycle is the major pathway for the metabolism and excretion of waste nitrogen from the body. (Ex. 1002 at ¶ 27.) In the urea cycle, enzymes and transporters synthesize urea from ammonia, and the urea is then excreted to remove excess nitrogen. (Ex. 1007 at [0005] and Fig. 1.) UCDs occur when enzymes or transporters in the urea cycle are deficient. (Ex. 1002 at ¶ 27.) These deficiencies can lead to elevated plasma ammonium levels and hyperammonemia, which can cause lethargy, coma, and even brain damage. (*Id.*; Ex. 1008 at 1.)

The applicant admitted during prosecution of the great-grandparent ’215 patent that it was “well known in the art that nitrogen retention disorders are

associated with elevated blood ammonia levels, and that these disorders can be treated by administering nitrogen scavenging drugs." (Ex. 1018 at 148.) It was also well known before the priority date of the '966 Patent that treatment options for treating UCDs included the use of nitrogen scavenging drugs such as sodium benzoate, sodium phenylbutyrate (also known as NaPBA), and HPN-100. (Ex. 1002 at ¶¶ 30-31; Ex. 1007 at [0015]–[0016], [0020]–[0021]; Ex. 1009 at 1389; Ex. 1020; Ex. 1021.) BUPHENYL® (sodium phenylbutyrate, NaPBA) was FDA-approved in 1996, and is indicated as adjunctive therapy in the chronic management of patients with certain UCDs. (Ex. 1020 at 3327.)

Because NaPBA is converted to phenylacetic acid ("PAA") in the body, it is referred to as a PAA prodrug. (Ex. 1007 at [0022]; Ex. 1002 at 32.) *In vivo*, NaPBA rapidly oxidizes to form one molecule of PAA, which in turn conjugates with glutamine to form phenylacetylglutamine ("PAGN"), which is then excreted in the urine. (Ex. 1009 at 1389; Ex. 1007 at [0003], [0021]–[0037]; Ex. 1002 ¶ 33.) Each molecule of PAGN carries away two molecules of nitrogen.

Because glyceryl tri-[4-phenylbutyrate] is converted to phenylbutyrate (PBA) in the body and then to PAA, it is also referred to as a PAA prodrug, or a PBA prodrug. (Ex. 1007 at [0023]; Ex. 1002 ¶ 32.) Glyceryl tri-[4-phenylbutyrate] is hydrolyzed by human pancreatic lipases to release three molecules of phenylbutyrate (PBA), which in turn are oxidized to form three

molecules of PAA and, in turn, three molecules of PAGN. (Ex. 1024 at 4:65-5:2.) Each molecule of glyceryl tri-[4-phenylbutyrate] therefore carries out six molecules of waste nitrogen (two nitrogen per PAGN molecule). (Ex. 1007 at [0022].)

It was well known before the priority date of the '966 Patent that treating patients with UCDs involved achieving a balance between diet, amino acid supplementation, and use of nitrogen scavenging drugs. (Ex. 1016 at S56; Ex. 1002 ¶ 35.) "The goal of treatment is to maintain normal levels of plasma ammonia through the use of the low-protein diet and medication while allowing for normal growth." (Ex. 1016 at S58; *see also* Ex. 1007 at, *e.g.*, [0182] (noting that subjects treated with HPN-100 can "achieve and maintain normal plasma ammonia levels").) Another critical aspect of therapy was monitoring fasting plasma ammonia levels, and if the levels were elevated, administering nitrogen scavenging drugs to decrease plasma ammonia values and bring and maintain them within normal ranges for the subject. (Ex. 1002 ¶¶ 36, 37, 39–40; Ex. 1007 at, *e.g.*, [0083], [0226]; Ex. 1004 at 1631, 1632 (Fig. 1); Ex. 1005 at 1118; Ex. 1006 at 273 (Table 11.9); Ex. 1008 at 10; Ex. 1015 at S11.) There is no minimum level of blood ammonia that must be maintained for normal body function. (Ex. 1002 ¶ 29.)

As will be discussed further below, the ’966 Patent describes nothing more than applying well known principles for treating UCD patients.

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

Petitioner certifies that (1) the ’966 Patent, issued on May 3, 2016, is available for IPR; and (2) Petitioner is not barred or estopped from requesting an IPR on the grounds identified in this Petition.

V. PAYMENT OF FEES (37 C.F.R. § 42.103)

Petitioner authorizes required fees to be charged to Deposit Acct. 506989.

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

A. Real Parties-in-Interest

Petitioner certifies that Lupin Ltd. and Lupin Pharmaceuticals Inc. are the real parties-in-interest.

B. Related Matters

On August 8, 2016 Horizon served Lupin Pharmaceuticals, Inc. and Lupin Ltd. with a complaint in the District Court for the District of New Jersey (Case No. 1:16-cv-04438) alleging infringement of the ’278 and ’966 Patents.

Horizon is also asserting the ’559 Patent against Lupin in the District of New Jersey (Case No. 1:15-cv-07624), and the ’215 Patent and the ’012 Patent against Par in the Eastern District of Texas (Case No. 2-14-cv-00384).

The ’559 Patent is the subject of Lupin’s IPR2016-00829, which was instituted and is pending.

The ’215 Patent was the subject of IPR2015-01127, filed by Par Pharmaceutical, Inc., to which IPR2016-00284, filed by Lupin, was joined. In a Final Written Decision dated September 29, 2016, the Board cancelled all claims of the ’215 Patent. See IPR2015-01127, Paper 49. Patent Owner has not appealed this decision.

Concurrently herewith, Lupin is filing an IPR on the ’278 Patent.

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

Lead counsel is Elizabeth J. Holland (Reg. No. 47,657), and backup counsel is Cynthia Lambert Hardman (Reg. No. 53,179), both of Goodwin Procter LLP, The New York Times Building, 620 Eighth Avenue, New York, NY 10018, (212) 813-8800 (telephone), (212) 355-3333 (facsimile). Counsels’ email addresses are eholland@goodwinlaw.com and chardman@goodwinlaw.com.

Please address all correspondence and service to counsel listed above. Petitioner consents to service by email at the above email addresses.

VII. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art (“POSA”) is a hypothetical person who is presumed to know all of the relevant prior art, has ordinary creativity, is not an automaton, and is capable of combining teachings of the prior art. *See KSR Int’l*

Co. v. Teleflex Inc., 550 U.S. 398, 420–21 (2007). Petitioner submits that a POSA is a physician with an M.D. degree, who did a residency in pediatrics or internal medicine, and who has specialized training in the treatment of UCDs and other nitrogen retention disorders. (Ex. 1002 ¶ 19.) A POSA would easily have understood the prior art references referred to herein and would have been capable of drawing inferences from them.

VIII. CLAIM CONSTRUCTION

The challenged claims should be given their broadest reasonable interpretation ("BRI") in light of the patent specification. 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). For purposes of this IPR only, Petitioner adopts the following constructions as the BRI of each term.

According to the specification, "upper limit of normal" ("ULN"), which appears in each of the challenged claims, means "the highest level in the range of normal values." (Ex. 1003 at 12:11–12.)

Each of independent claims 1, 6, 9, and 12, as well as dependent claims 4, 7, 10, and 13, recite a "fasting" plasma ammonia level. In the medical context, the plain and ordinary meaning of the term "fast" means abstaining from food. *See, e.g.*, Stedman's Medical Dictionary (Lippincott Williams & Wilkins 2006) (Ex. 1019). The specification of the '966 Patent

is consistent with this, making clear that fasting means that the subject preferably does not ingest any food, and in certain embodiments, some non-food substances (such as certain supplements, beverages, etc.):

> During the fasting period, the subject preferably does not ingest any food. In certain embodiments, the subject may also refrain from ingesting certain non-food substances during the fasting period. For example, in certain embodiments the subject does not ingest any supplements and/or nitrogen scavenging drugs during the fasting period. In certain of these embodiments, the subject may nonetheless ingest one or more drugs other than nitrogen scavenging drugs during the fasting period. In certain embodiments, the subject does not ingest any high calorie liquids during the fasting period. In certain of these embodiments, the subject does not ingest any liquids other than water during the fasting period. In other embodiments, the subject may ingest small amounts of low calorie beverages, such as tea, coffee, or diluted juices.

(Ex. 1003, at 10:30–44.) The patent specifies that the fasting period is at least four hours:

> In certain embodiments of the methods disclosed herein, the fasting period for obtaining a fasting blood ammonia level is overnight. In certain

> embodiments, the fasting period is 4 hours or more, 5 hours or more, 6 hours or more, 7 hours or more, 8 hours or more, 9 hours or more, 10 hours or more, 11 hours or more, or 12 hours or more, and in certain embodiments the fasting period is 4-8 hours, 6-8 hours, or 8-12 hours.

(*Id.*, at 10:23–29.) In view of specification and the plain and ordinary meaning of the term fasting, "fasting" plasma ammonia level means a plasma ammonia level from a person who has not eaten food for at least four hours.

Claims 1, 6, and 9 require that the "adjusted dosage" is "***greater than*** the initial dosage." With regard to an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is ***greater than*** the initial dosage, the specification states: "Increasing the dosage of a nitrogen scavenging drug may refer to increasing the amount of drug per administration (*e.g.*, an increase from a 3 mL dosage to a 6 mL dosage), increasing the number of administrations of the drug (*e.g.*, an increase from once-a-day dosing to twice- or three-times-a-day), or any combination thereof." (*Id.* at 10:10–15.) In view of this disclosure, an adjusted dosage that is "***greater than*** the initial dosage" means a dosage that increases the amount of drug per administration, an increased number of administrations of the drug, or any combination thereof.

Claim 12 requires that the "adjusted dosage" is the same as the initial effective dosage or is an "***increased*** dosage." As discussed above, with regard to

an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is ***increased***, the specification states: "Increasing the dosage of a nitrogen scavenging drug may refer to increasing the amount of drug per administration (*e.g.*, an increase from a 3 mL dosage to a 6 mL dosage), increasing the number of administrations of the drug (*e.g.*, an increase from once-a-day dosing to twice- or three-times-a-day), or any combination thereof." (*Id.* at 10:10–15.) In view of this disclosure, an adjusted dosage that is an "***increased*** dosage" means a dosage that increases the amount of drug per administration, an increased number of administrations of the drug, or any combination thereof.

In addition, each of the challenged claims contains the transition term "comprising." Accordingly, while the claims require the claimed method steps, they do not exclude additional steps.

For purposes of this IPR only, Petitioner will assume that the claims' preambles are limiting.

Petitioners' positions regarding the scope of the claims should not be construed as an assertion regarding the appropriate claim scope in other adjudicative forums, where a different claim interpretation standard may apply.

IX. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE (37 C.F.R. §§ 42.22(a) and 42.104(b))

In Ground 1, Petitioner requests IPR and cancellation of claims 12, 14, and 15 as unpatentable under 35 U.S.C. § 102 as anticipated by the *'859 Publication*.

In Ground 2, Petitioner requests IPR and cancellation of claims 1-15 as unpatentable under 35 U.S.C. § 103 as obvious over *Blau*, *Simell*, and the *'859 Publication*.

Petitioner provides the declaration of Keith Vaux, M.D., an expert in the field, in support of this petition. (Ex. 1002 ¶¶ 1–4; Ex. 1023.)

A. Overview of Prior Art

Simell (Ex. 1005) was published in 1986, and qualifies as prior art under 35 U.S.C. § 102(b). It discloses methods of administering the nitrogen scavenging drugs sodium benzoate and phenylacetate to children with lysinuric protein intolerance, which *Simell* specifies is a type of UCD, following the standardized induction of hyperammonemia. (Ex. 1002 ¶ 48; Ex. 1005 at Abstract, 1117–18.) As part of the protocol, *Simell* measured fasting blood ammonia levels in the patients after an overnight fast. (Ex. 1005 at 1118.)

Blau (Ex. 1006) was published in 1996, and qualifies as prior art under 35 U.S.C. § 102(b). *Blau* is a physician's guide to the laboratory diagnosis of metabolic diseases, including UCDs. (Ex. 1006 at, *e.g.*, 1, Ch. 11.) *Blau* discloses "**Specimen Collection**" guidelines that require ammonia levels to be measured "at least 4 h after end of the last meal or stopping intravenous [amino acid] supply from a central vein or artery." (Ex. 1006 at 273 (Table 11.9).) A POSA would have understood *Blau* to suggest measuring fasting blood ammonia levels. (Ex.

1002 ¶ 49.) *Blau* discusses different types of UCDs and laboratory tests that should be performed when treating a UCD patient. (Ex. 1006 at 261, 270–71, 273 (Table 11.9).)

The *'859 Publication* is the publication for Horizon's '012 Patent. (Ex. 1007.) It published on January 14, 2010, and qualifies as prior art under 35 U.S.C. § 102(b).

The *'859 Publication* teaches the oral administration of nitrogen scavenging drugs to patients with nitrogen retention disorders, including UCDs. (*See, e.g.*, Ex. 1007 at [0002], [0020]–[0021], [0189]; Ex. 1002 ¶ 73.) These nitrogen scavenging drugs can be PAA prodrugs, such as HPN-100 or NaPBA. (Ex. 1007 at [0144]–[0156], [0221]–[0229].) HPN-100 is a preferred embodiment, and is described as providing better control of ammonia levels than NaPBA in a clinical study of UCD patients. (*Id.* at [0036], [0060], [0137], [0202]–[0203], [0209], Figs. 12, 13.)

The *'859 Publication* states that an initial dosage of a PAA prodrug (such as HPN-100) "can be calculated by methods known in the art once a patient's dietary intake of protein is known, and assuming the patient has a relatively normal liver function." (*Id.* at [0079].) It also teaches methods of adjusting the dose of HPN-100 in UCDs, based in part on evaluating plasma ammonia levels. (*Id.* at [0020]–[0022], Example 3, [0088]–[0092], [0095]–[0099], [0107]–[0108], [0226], [0232].) One such method provides: (a) administering an initial dosage of a PAA prodrug

according to the patient's dietary protein load; (b) measuring the amount of total waste nitrogen excreted following administration of the drug; (c) measuring blood ammonia to determine if the increase in urinary excretion of total waste nitrogen is sufficient to control blood ammonia levels; and (d) adjusting the initial dosage to provide an adjusted dosage of the drug based upon ammonia control, dietary protein, and the amount of total waste nitrogen excreted, or the amount of waste PAGN excreted. (*Id.* at [0088]–[0091].)

To determine whether a patient's plasma ammonia levels are acceptable, the *'859 Publication* teaches comparing a plasma ammonia level to the ULN of plasma ammonia for the subject, and notes that the ULN can vary but is typically below about 40 μmol/L. (*Id.* at [0063, [0094], [0201]; Ex. 1002 ¶ 44.) It also discloses that the plasma ammonia level can help assess the effectiveness of the overall drug and dietary regimen for a particular patient. (Ex. 1007at [0083], [0088]–[0092], [0095]–[0099], [0226], [0232].) If the ammonia control is inadequate, the dosage of the nitrogen scavenging drug may be increased. (*Id.* at [0083], [0232]; Ex. 1002 ¶ 44.)

The *'859 Publication* describes a clinical study of 10 adult UCD patients who were switched from NaPBA to a PBA-equimolar dose of glyceryl tri-[4-

phenylbutyrate].[1] (*Id.* at [0195]-[0209].) In the study, the blood ammonia levels of the patients were first recorded while the patients were taking stable doses of NaPBA. (*Id.* at [0195].) The patients were then converted to a PBA-equimolar dose of HPN-100. (*Id.*) Once the patients reached steady-state on HPN-100, their ammonia values were again recorded. (*Id*.) For both drugs, the publication reports the drug dosage, the maximum observed ammonia value (Cmax), and the time-normalized area under the curve (TN-AUC) ammonia value for each patient. (*Id.* at table following [0201]; *see also* Ex. 1002 at ¶¶ 45-47 for a summary of the clinical study.)

As stated in the publication, the ULN for venous ammonia varied among the study sites from 26 to 35 µmol/L. (Ex. 1007 at [0201].) When taking HPN-100, many of the patients had TN-AUC ammonia values under 35 µmol/L (the maximum ULN at any of the study sites), and one patient (Subject 1006) had a TN-AUC ammonia level of 8.30 µmol/L, which was less than half the ULN (whether the ULN was 26 µmol/L, 35 µmol/L, or somewhere in between). (*Id.* at table following [0201]; Ex. 1002 at ¶ 46, 63.) This same patient also had an

[1] Given that both NaPBA and glyceryl tri-[4-phenylbutyrate] are PAA prodrugs, it was known that dosages of glyceryl tri-[4-phenylbutyrate] could be calculated based on an PBA-equimolar amount of NaPBA. (*See, e.g.*, Ex. 1007 at [0025-0026], [0231].)

ammonia Cmax of 13.0 μmol/L, which is also at or below half the ULN (whether the ULN was 26 μmol/L, 35 μmol/L, or somewhere in between). (Ex. 1007 at table following [0201]; Ex. 1002 at ¶ 46, 63.) When this patient was taking NaPBA, the corresponding ammonia values were much higher (Cmax of 150 μmol/L, TNAUC of 71.5 μmol/L). (Ex. 1007 at table following [0201]; Ex. 1002 at ¶ 46, 63.)

The publication reports that no patients experienced serious adverse events with HPN-100. (Ex. 1007 at [0203], *see also* [0086].) The *'859 Publication* also explains that after the PAA prodrug is administered, urinary PAGN excretion may be measured, and the dosage of HPN-100 may be adjusted based on PAGN output. (Ex. 1007 at, *e.g.*, [0224]-[0227].)

B. Ground 1: Claims 12, 14, and 15 are Anticipated By the '859 Publication

The *'859 Publication*, summarized above, discloses each and every limitation of claims 12, 14, and 15. Claim 12 reads as follows:

> 12. A method of treating a patient having a urea cycle disorder comprising:
>
> (a) administering an initial effective dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) to the patient, wherein the initial effective dosage is calculated based on body surface area of the patient;

(b) measuring the patient's urinary PAGN and/or fasting plasma ammonia level to determine whether to change the dosage of the glyceryl tri-[4-phenylbutyrate] (HPN-100); and

(c) administering a subsequent effective dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) to the patient that is either the same as the initial effective dosage or is an increased dosage, wherein said increased dosage, if any, is calculated based on the patient's urinary PAGN and/or fasting plasma ammonia level.

Claims 14 and 15 add that the initial (claim 14) and subsequent (claim 15) effective dosages of glyceryl tri-[4-phenylbutyrate] are administered orally.

With regard to the preamble and part (a) of claim 12, the *'859 Publication* teaches a method of treating a patient who has a urea cycle disorder comprising administering an initial effective dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) to the patient, wherein the initial effective dosage is calculated based on body surface area of the patient. Specifically, the *'859 Publication* provides that when a UCD patient is being switched from NaPBA to glyceryl tri-[4-phenylbutyrate], that patient can be switched to a dosage of glyceryl tri-[4-phenylbutyrate] that does not exceed the recommended dosing levels for NaPBA. (Ex. 1007 at [0084].) The label for the use of NaPBA for the chronic treatment of UCDs recommends a daily dosage range that is based on body surface area (g/m^2), and the *'859 Publication*

similarly provides corresponding dosages of HPN-100 that are calculated according to body surface area. (*Id.*, "For a subject weighing more than 20 kg, a dosage range for HPN-100 would be between 8.6 and 11.2 mL/m^2.")

The *'859 Publication* also discloses part (b) of claim 12, which recites: "measuring the patient's urinary PAGN and/or fasting plasma ammonia level to determine whether to change the dosage of the glyceryl tri-[4-phenylbutyrate] (HPN-100)." Specifically, the *'859 Publication* provides a "method to monitor the effectiveness of a treatment of a UCD patient with HPN-100, where monitoring consists of, or consists essentially of, monitoring the patient's urinary PAGN excretion and/or plasma ammonia levels." (Ex. 1007 at [0085].)

The *'859 Publication* also discloses part (c) of claim 12, which recites: "(c) administering a subsequent effective dosage of glyceryl tri-[4-phenylbutyrate] (HPN-100) to the patient that is either the same as the initial effective dosage or is an increased dosage, wherein said increased dosage, if any, is calculated based on the patient's urinary PAGN and/or fasting plasma ammonia level." Specifically, the *'859 Publication* states that "If the ammonia control is inadequate, the dosage of the nitrogen scavenging drug may need to be increased if that can be done, or the patient's dietary protein intake can be decreased if that is feasible." (*Id.* at [0083].)

With regard to claims 14 and 15, the *'859 Publication* also states that the disclosed methods relate to oral administration of glyceryl tri-[4-phenylbutyrate]. (*Id.* at [0020]–[0021], [0002].)

A patent claim is invalid as anticipated if every limitation in a claim is found in a single prior art reference. *Impax Labs. Inc. v. Aventis Pharms. Inc*., 468 F.3d 1366, 1381 (Fed. Cir. 2006). Here, the *'859 Publ*ication discloses each and every limitation of claims 12, 14, and 15, and thereby anticipates these claims. Furthermore, the *'859 Publication* is enabling because it describes the claimed methods of treatment with sufficient detail such that a POSA would be able to carry out the claimed methods. *Id*. at 1383 ("the proper issue is whether the . . . [prior art] is enabling in the sense that it describes the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention"). Indeed, as is clear from the*'859 Publication* itself, persons of ordinary skill in the art knew how to administer glyceryl tri-[4-phenylbutyrate] to patients and how to monitor their blood ammonia levels. (*See* Ex. 1007 at Example 3, describing clinical study.) Adjusting the dose of the drug to achieve more ammonia control was also well-known to POSAs. (*See, e.g.*, *id.* at [0083].) Accordingly, claims 12, 14, and 15 are unpatentable as anticipated by the*'859 Publication*.

C. Ground 2: Claims 1-15 are Unpatentable as Obvious Over *Blau*, *Simell*, and the *'859 Publication*, in View of the POSA's Knowledge

1. Overview of Applied Prior Art

Blau, *Simell* and the *'859 Publication* are reviewed in Section IX(A) above.

2. Motivation to Combine Applied Prior Art

A POSA administering or adjusting the dosage of a nitrogen scavenging drug in a UCD patient before the priority date would have been motivated to combine the teachings of *Blau*, *Simell*, and the *'859 Publication* to arrive at the claimed subject matter. (Ex. 1002 ¶¶ 112–117.)

Simell discusses methods of administering nitrogen scavenging drugs, specifically sodium benzoate and phenylacetate, to lower blood ammonia levels in patients with lysinuric protein intolerance, which *Simell* specifies is a type of UCD. (Ex. 1005 at Abstract, 1117–18.) A POSA reading *Simell*, which includes measuring plasma ammonia levels, would have been motivated to combine its teachings with *Blau*, which teaches that when treating UCD patients, ammonia levels should be measured when the patient is fasting. (Ex. 1002 ¶ 114.) Indeed, a POSA would have known that because ammonia levels vary throughout the day and in response to ingestion of protein (which can vary from day to day), baseline blood samples should be taken from a fasted patient, at the same time of day, and under the same circumstances each time, to ensure that treatment decisions are made based on the most accurate and consistent information. (Ex. 1002 ¶ 114; see

also Ex. 1006 at 268, Table 11.5 (noting that postprandially, ammonia levels will be 30-60 μmol/L higher depending on time and nitrogen load); Ex. 1012 at 213 (noting diurnal fluctuation of blood ammonia level in UCD patient); Ex. 1017 at 164, Table II (noting effect of protein ingestion on plasma ammonia levels over time); Ex. 1015 at S11, S19.)

Moreover, a POSA treating UCD patients would have looked to the *'859 Publication* for guidance on choosing an effective dosage of the nitrogen scavenging drug, as well as guidance on adjusting the dosage of the nitrogen scavenging drug administered. (Ex. 1002 ¶ 115; Ex. 1007 at Abstract.)

The Federal Circuit has held that motivation to combine can be found in many different forms, including, as here, in the testimony of an expert. *See Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1294 (Fed. Cir. 2006) (motivation to combine may be implicitly stated in the prior art and supported by testimony of an expert witness regarding knowledge of a POSA). As Dr. Vaux explains, a POSA interested in UCD treatment with nitrogen scavenging drugs would have referred to the *'859 Publication* for methods of using glyceryl tri-[4-phenylbutyrate], would have referred to *Simell* for specific clinical protocols for using nitrogen scavenging drugs in some UCD patients, and would have additionally referred to *Blau* for guidance on measuring fasting blood ammonia levels. (Ex. 1002 ¶¶ 114-117.)

3. Independent Claims 1, 6, and 9

Independent claims 1, 6, and 9 would have been obvious based on the teachings of *Blau*, *Simell*, and the *'859 Publication*, in view of the POSA's knowledge. (Ex. 1002 ¶¶ 118-136.)

(a) Preambles of Independent Claims 1, 6, and 9

Independent claims 1, 6, and 9 are generally directed to a method of adjusting a dosage of glyceryl tri-[4-phenylbutyrate] in a UCD subject who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] by taking into account the subject's fasting plasma ammonia levels.

The *'859 Publication* teaches methods of treating UCD patients with glyceryl tri-[4-phenylbutyrate], methods of monitoring the effectiveness of such treatment, and methods of adjusting dosage based in part on plasma ammonia values.[2] (Ex. 1007 at, *e.g.*, [0088]–[0092], [0095]–[0099], [0107]–[0108], [0226],

[2] Notwithstanding the disclosure of such methods, the *'859 Publication* also asserts that use of plasma ammonia levels to assess disease control in UCD patients is often inconvenient, and in one spot expresses a preference for adjusting an initial dose without using plasma ammonia levels (in favor of using an allegedly novel approach of adjusting dose based on a different biomarker, urinary PAGN), which Patent Owner may argue "teaches away" from the claimed subject matter. (*See, e.g.*, Ex. 1007 at [0073], [0099], [0020].) Nevertheless, the *'859 Publication*

[0232]; Ex. 1002 ¶ 119.) Specifically, the *'859 Publication* teaches that if ammonia control is inadequate, the dose of the drug can be increased. (Ex. 1007 at [0083]; Ex. 1002 ¶ 119.)

The preambles of claims 1, 6, and 9 also specify that the claimed method is carried out on a subject "who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level." (Ex. 1003 at 24:13-14, 24:40–41, 24:59–60.) Maintenance of plasma ammonia levels within normal limits, and below the ULN, is one of the objectives of therapy with nitrogen scavenging drugs. (*See, e.g.*, Ex. 1020 at 3327 ("Laboratory Tests" section, noting that plasma levels of ammonia "should be maintained within normal limits"); Ex. 1007 at [0083], [0046] (noting desire to "maintain a stable level of plasma ammonia," [0074] (noting that plasma ammonia levels less than ULN indicate effective treatment), [0182] (noting that subjects treated with HPN-100 in the disclosed methods will typically "achieve and maintain normal plasma ammonia levels"), [0209] (discussing "superior control of ammonia" and consistent reduction of ammonia

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clearly discloses the use of plasma ammonia levels in adjusting drug dose. (Ex. 1002 at ¶ n. 6.) Further, a POSA would have known that a patient's plasma ammonia level is a critical parameter for tracking effectiveness of an overall treatment program, and would have continued to measure and use plasma ammonia levels in making treatment decisions. (*See* Ex. 1007 at [0039]; Ex. 1002 at ¶ n. 6.)

levels to below about 40 µmol/L), [0226] (noting that "[d]ietary protein intake or drug dosage or both could be adjusted to attain a normal or desired plasma ammonia level, e.g. a level below about 40 µmol/L"); Ex. 1002 ¶¶ 120; Ex. 1016 at S58.)

Ammonia levels were known to vary throughout the day, including, for example, by increasing after the ingestion of food. (*See, e.g.*, Ex. 1002 at ¶¶ 121; Ex. 1006 at 268, Table 11.5 (noting that postprandially, ammonia levels will be 30-60 µmol/L higher depending on time and nitrogen load); Ex. 1012 at 213 (noting diurnal fluctuation of blood ammonia level in UCD patient); Ex. 1017 at 164, Table II (noting effect of protein ingestion on plasma ammonia levels over time); Ex. 1016 at S58; Ex. 1015 at S19.)

Accordingly, in order to maintain a patient's plasma ammonia levels within normal limits, a POSA would have been motivated to administer more drug to reduce ammonia levels even in cases where the fasting plasma ammonia level was above half the ULN but below the ULN. (Ex. 1002 at ¶ 122.) For example, in the case of a patient with a fasting plasma ammonia level approaching the ULN, a POSA would have desired to maintain the patient at normal ammonia levels, and would have known that variation in ammonia levels due to time of day and/or ingestion of food would potentially take the patient outside of normal levels. (Ex. 1002 at ¶ 122.) Thus, even though the patient's fasting plasma ammonia level was

already below the ULN, a POSA would have been motivated to increase the dose of drug to lower the patient's baseline ammonia and to help ensure that the patient routinely stayed within normal plasma ammonia limits. (Ex. 1002 at ¶ 122; *see also* Ex. 1007 at [0226] (suggesting adjustment of drug dosage to "attain a normal or desired plasma ammonia level, *e.g.*, a level below about 40 μmol/L").)

The preamble of claim 6 further specifies that the subject is a pediatric subject, whereas the preamble of claim 9 further specifies that the subject is an adult. The prior art teaches the administration of nitrogen scavenging drugs to both children and adults. (*See, e.g.*, Ex. 1007 at [0195] (administering nitrogen scavenging drugs to adults); Ex. 1004 at 1633 (administering nitrogen scavenging drugs to children); Ex. (1005) (same); Ex. 1007 at [0016] (recognizing that ammonia scavenging drugs are particularly appropriate for children); Ex. 1002 at ¶ 123.) Thus, a POSA would have been motivated to treat both children and adults with nitrogen scavenging drugs such as glyceryl tri-[4-phenylbutyrate]. (Ex. 1002 at ¶ 123.)

(b) Part (a) of Independent Claims 1, 6, and 9

Part (a) of claims 1, 6, and 9 recites "measuring a fasting plasma ammonia level for the subject."

Blau teaches that blood collection for measuring plasma ammonia levels in UCD patients should be performed at least four hours after the end of the last

meal.[3] (Ex. 1006 at 273 (Table 11.9); Ex. 1002 ¶ 126.) Therefore, a POSA reading the *'859 Publication* in view of *Blau* would have understood that the blood for the ammonia measurement should be collected at least four hours after the end of the last meal, which would provide a fasting blood ammonia level.[4] (Ex. 1002 ¶ 126; *see also* n.7.)

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[3] The '966 Patent states the "fasting period" for obtaining a fasting blood ammonia level can be 4 hours or more and that "[d]uring the fasting period, the subject preferably does not ingest any food." (Ex. 1003 at 10:25–31.)

[4] To the extent Patent Owner argues that *Blau* relates solely to using fasting plasma ammonia levels for diagnosing UCDs but not for treating them, this purported criticism should be rejected. Prior to September 2011, it was routine for practitioners to obtain fasting blood samples on which to perform ammonia testing, no matter what the purpose of the testing (*e.g.* for both treatment and diagnosis). This is confirmed by Ex. 1015 at S11, as well as by Ex. 1010. *See also* Ex. 1002 at n.7. Exhibit 1010, a Lab Update concerning "Measurement of Ammonia in Blood," was published by UMass Memorial Medical Center in Worcester, Massachusetts, in February 2007. Exhibit 1010 specifies that for measurement of blood ammonia, most methods recommend collecting a sample from patients who have fasted for at least 6 hours. (*Id.*; Ex. 1002 at n. 7.) It also teaches that measurements should be taken at the same time of day and under the same

Additionally, as evidenced by *Simell*, it was well known in the art before the '966 Patent's priority date to measure fasting blood ammonia levels when treating UCD patients with nitrogen scavenging drugs. (Ex. 1005 at 1118; Ex. 1002 ¶ 127.) *Simell* discloses that the treated patients underwent an overnight fast and then had their blood ammonia levels measured prior to infusion of the nitrogen scavenging drug. (Ex. 1005 at 1118, Fig. 1; Ex. 1002 ¶ 127.) Therefore, a POSA reading the *'859 Publication* in view of *Blau* and *Simell* would have understood the need to measure a fasting plasma ammonia level. (Ex. 1002 ¶ 127; Ex. 1005 at 1118; Ex. 1006 at 273 (Table 11.9).)

(c) Part (b) of Independent Claims 1, 6, and 9

Part (b) of claims 1, 6, and 9 recites "comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level."

Maintenance of plasma ammonia levels within normal limits, and below the ULN, is one of the objectives of therapy with nitrogen scavenging drugs. (*See, e.g.*, Ex. 1020 at 3327 ("Laboratory Tests" section, noting that plasma levels of ammonia "should be maintained within normal limits"); Ex. 1007 at [0083], [0046] (noting desire to "maintain a stable level of plasma ammonia," [0074] (noting that

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circumstances, due to a diurnal variation in blood ammonia levels. (Ex. 1010; Ex. 1002 n. 7.)

plasma ammonia levels less than ULN indicate effective treatment), [0182] (noting that subjects treated with HPN-100 in the disclosed methods will typically "achieve and maintain normal plasma ammonia levels"), [0209] (discussing "superior control of ammonia" and consistent reduction of ammonia levels to below about 40 μmol/L), [0226] (noting that "[d]ietary protein intake or drug dosage or both could be adjusted to attain a normal or desired plasma ammonia level, e.g. a level below about 40 μmol/L"); Ex. 1002 ¶¶ 120; Ex. 1016 at S58.)

It was known to use ammonia to guide drug dosing decisions, and to do so by comparing the patient's fasting plasma ammonia level to the ULN to assess ammonia control. (*See, e.g.*, Ex. 1007 at [0088]-[0092], [0226], [0232].)

The *'859 Publication* states that plasma levels of ammonia are acceptable when they are at or below a level considered normal for the subject, and that this would commonly mean that the plasma ammonia level is below about 40 μmol/L. (Ex. 1007 at [0094].) The *'859 Publication* further states that "In certain clinical tests described herein the upper limit of normal for the subjects was between 26 and 35 μmol/L, and it is recognized in the art that a normal ammonia level will vary depending upon exactly how it is measured." (*Id.*) A POSA reading the *'859 Publication* would have understood that the ULN is about 35 μmol/L, and may vary based on how it is measured. (Ex. 1002 ¶ 130; Ex. 1007 at [0094], [0201], [0063] & Fig. 13.) The *'859 Publication* also states that if the ammonia control is

inadequate, the dosage of the nitrogen scavenging drug may be increased. (*Id.* at [0083], [0232]; Ex. 1002 ¶ 130.) Accordingly, a POSA reading the *'859 Publication* would have understood that the patient's fasting plasma ammonia level should be compared to the ULN for plasma ammonia level to determine the next step in treatment. (Ex. 1002 ¶ 130.)

(d) Part (c) of Independent Claims 1, 6, and 9

Part (c) of claims 1, 6, and 9 recites "administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level."

The *'859 Publication* instructs that the dose of a nitrogen scavenging drug can be adjusted based upon ammonia control, with the aim of obtaining plasma levels of ammonia at or below a level considered normal for the subject. (Ex. 1007 at [0091], [0092], [0094], [0095]–[0099], [0026]; Ex. 1002 ¶ 132.) A POSA reading *Blau*, *Simell*, and the *'859 Publication* would have administered a dose of glyceryl tri-[4-phenylbutyrate] greater than the initial dose if the measured fasting blood ammonia level was greater than half the ULN. (Ex. 1002 ¶ 132.) The *'859 Publication* taught that if ammonia control is inadequate—*i.e.* above a level

considered normal for the subject[5]—the dose of the drug may need to be increased. (Ex. 1007 at [0083], [0094]; Ex. 1002 ¶ 133.)

Again, the goal of nitrogen scavenging therapy for UCD patients is to maintain a stable, normal plasma ammonia level in a subject. (*See, e.g.*, Ex. 1020 at 3327 ("Laboratory Tests" section, noting that plasma levels of ammonia "should be maintained within normal limits"); Ex. 1007 at [0083], [0046] (noting desire to "maintain a stable level of plasma ammonia," [0074] (noting that plasma ammonia levels less than ULN indicate effective treatment), [0182] (noting that subjects treated with HPN-100 in the disclosed methods will typically "achieve and maintain normal plasma ammonia levels"), [0209] (discussing "superior control of

[5] A person of ordinary skill in the art would have known that the ULN varies by patient, *e.g.*, based on their age. For example, *Blau* provides ULN reference values of 80 μmol/L for neonates and 50 μmol/L for 4-month olds. (Ex. 1006 at 273 (Table 11.5).) In the *'859 Publication*, the ULN in the described clinical tests was between 26 and 35 μmol/L, and is characterized as generally below about 40 μmol/L. (Ex. 1007 at [0094].) In *Simell*, the ULN was at least 70 μmol/L in patients with ages ranging from 2.7 to 12.6 years old. (Ex. 1005 at 1117–18.) In *Brusilow '84*, the ULN was 35 μmol/L. (Ex. 1004 at 1631–32.) *See* Ex. 1002 at n. 8. It was also known that the ULN varies depending on how it is measured and depending on the lab that performs the testes. (Ex. 1007 at [0094], [0201].)

ammonia" and consistent reduction of ammonia levels to below about 40 µmol/L), [0226] (noting that "[d]ietary protein intake or drug dosage or both could be adjusted to attain a normal or desired plasma ammonia level, e.g. a level below about 40 µmol/L"); Ex. 1002 ¶¶ 120; Ex. 1016 at S58.) Claims 1, 6, and 9 merely recognize the known premise that increasing the dosage of a nitrogen scavenging drug will decrease plasma ammonia levels. (*See, e.g.*, Ex. 1007 at [0083]; Ex. 1002 ¶ 133.) A POSA would have desired to maintain the patient at normal ammonia levels, and would have known that variation in ammonia levels due to time of day and/or ingestion of food would potentially take the patient outside of normal levels. (Ex. 1002 at ¶ 134; Ex. 1006 at 268, Table 11.5 (noting that postprandially, ammonia levels will be 30-60 µmol/L higher depending on time and nitrogen load); Ex. 1012 at 213 (noting diurnal fluctuation of blood ammonia level in UCD patient); Ex. 1017 at 164, Table II (noting effect of protein ingestion on plasma ammonia levels over time); Ex. 1016 at S58; Ex. 1015 at S19.) Thus, for a patient with fasting plasma ammonia levels approaching the ULN, a POSA would have been motivated to increase the dose of drug to lower the patient's baseline ammonia and to help ensure that the patient routinely stayed within normal plasma ammonia limits. (Ex. 1002 at ¶ 134.)

(e) Additional Limitation of Claim 1

Claim 1 further specifies that the ULN for plasma ammonia level is in the range of 26–64 μmol/L. As stated above, commonly-used ULNs for plasma ammonia were 35 and 40 μmol/L, which fall within the claimed range, and the range of 26-35 was expressly disclosed in the prior art. (*See, e.g.*, Ex. 1002 ¶ 135; Ex. 1007 at [0094], [0201].) Therefore, a POSA would have known these to be reasonable ULNs achieved at various labs, and would have been motivated to use them.

Based on the teachings of *Blau*, *Simell*, and the *'859 Publication*, as well as the knowledge of a POSA, a POSA would have been motivated to carry out the method of claims 1, 6, and9, and would have had a reasonable expectation of success in doing so. The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention. *See, e.g.*, *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360-61 (Fed. Cir. 2007). Here, the claimed methods are merely comprised of well-known steps, and do not specify any particular efficacy measurements. (Ex. 1002 ¶ 136.) Accordingly, the claims are unpatentable as obvious. (Ex. 1002 ¶ 66.) (Ex. 1002 ¶ 136.)

4. Independent Claim 12

Claim 12 recites a method of treating a UCD patient that begins by administering an initial effective dosage of glyceryl tri-[4-phenylbutyrate] to the patient, wherein the dosage is calculated based on the body surface area of the patient.

As Dr. Vaux states, methods of calculating a dosage of glyceryl tri-[4-phenylbutyrate] based on body surface area were well-known in the art. (Ex. 1002 at ¶ 138.) For example, in disclosing how to convert a patient from NaPBA to a PBA-equivalent dose of HPN-100, the *'859 Publication* provides the doses of both drugs based on body surface area. (*See* Ex. 1007, table under [0026]; *see also* table under [0038] (disclosing dose in healthy volunteers based on body surface area); [0084] (stating that "For a subject weighing more than 20 kg, a dosage range for HPN-100 would be between 8.6 and 11.2 mL/m^2.").) Additionally, other nitrogen-scavenging drugs, such as AMMONUL, were also administered based on body surface area. (Ex. 1021 at 3326 (Dosage and Administration and Table 3)..) Accordingly, a POSA would have known that calculating a dose using body surface area was a method used in the art, and would have been motivated to use such a calculation. (Ex. 1002 at ¶ 138.)

Claim 12 also recites measuring the patient's urinary PAGN and/or fasting plasma ammonia level to determine whether to change the dosage, and

administering a subsequent effective dosage that is the same or increased, wherein an increased dosage is calculated based on the patient's urinary PAGN and/or fasting plasma ammonia levels. Adjusting drug dosage based on fasting plasma ammonia levels was well-known. (Ex. 1007 at, *e.g.*, [0088]–[0092], [0095]–[0099], [0107]–[0108], [0226], [0232]; Ex. 1002 at ¶ 139 . Additionally, as confirmed by Dr. Vaux, the *'859 Publication* teaches that after the PAA prodrug such as glyceryl tri-[4-phenylbutyrate] is administered, the urinary PAGN excretion may be measured, and the dosage of HPN-100 may be adjusted based on PAGN output. (Ex. 1007 at, *e.g.*, [0224], [0227], Ex. 1002 at ¶ 139.) Accordingly, a POSA would have known that determining whether to administer an adjusted dosage of drug based on urinary PAGN and/or fasted plasma ammonia levels was well-known, and that calculating an adjusted dosage based on urinary PAGN and/or fasting plasma ammonia levels was also well-known, would have been motivated to use such a calculation. (Ex. 1002 at ¶ 139.)

Based on the teachings of *Blau*, *Simell*, and the *'859 Publication*, as well as the knowledge of a POSA, a POSA would have been motivated to carry out the method of claim 12, and would have had a reasonable expectation of success in doing so. The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention. *See, e.g.*, *PharmaStem Therapeutics, Inc.*, 491 F.3d at 1360-61.

Here, the claimed method is merely comprised of well-known steps, and does not specify any particular efficacy measurements. (Ex. 1002 ¶ 140.) Accordingly, independent claim 12 is unpatentable as obvious. (Ex. 1002 ¶ 140.)

5. Dependent Claims 2 and 3

Claim 2 depends from claim 1, and recites that the ULN for plasma ammonia level is in the range of 32-38 μmol/L. Claim 3 depends from claim 2, and recites that the ULN for plasma ammonia level is in the range of 34-36 μmol/L.

As Dr. Vaux explains, these were standard values for the ULN of ammonia that would have been familiar to those of ordinary skill in the art as of September 2011. (Ex. 1002 ¶ 141.) For example, the *'859 Publication* teaches that the ULN varied between 26 and 35 μmol/L in a clinical test, depending on the study site. (Ex. 1007 at [0094], [0201].) This disclosure encompasses the claimed ranges. Therefore, a POSA would have understood that the ULN may vary depending on how it is measured, and it was known before the priority date of the '966 Patent that a ULN plasma ammonia level reasonably may be with the claimed ranges of 32-38 or 34-36 μmol/L. (Ex. 1002 ¶ 141.)

6. Dependent Claims 4, 7, 10, and 13

Dependent claims 4, 7, 10, and 13 depend from claims 1, 6, 9, and 12, respectively, and further require repeating the claimed steps ((a)-(c) for claims 4, 7,

and 10, and (b)-(c) for claim 13) until the subject exhibits a fasting plasma ammonia level at or below half the ULN for plasma ammonia level.

As discussed, maintenance of plasma ammonia levels within normal limits is one of the objectives of therapy with nitrogen scavenging drugs. (*See, e.g.*, Ex. 1020 at 3327 ("Laboratory Tests" section, noting that plasma levels of ammonia "should be maintained within normal limits"); Ex. 1007 at [0083], [0046] (noting desire to "maintain a stable level of plasma ammonia," [0074] (noting that plasma ammonia levels less than ULN indicate effective treatment), [0182] (noting that subjects treated with HPN-100 in the disclosed methods will typically "achieve and maintain normal plasma ammonia levels"), [0209] (discussing "superior control of ammonia" and consistent reduction of ammonia levels to below about 40 μmol/L), [0226] (noting that "[d]ietary protein intake or drug dosage or both could be adjusted to attain a normal or desired plasma ammonia level, e.g. a level below about 40 μmol/L"); Ex. 1002 ¶¶ 120; Ex. 1016 at S58. There is no minimum level of blood ammonia that must be maintained for normal body function. (Ex. 1002 ¶ 142.)

Ammonia levels were known to vary throughout the day, including, for example, by increasing after the ingestion of food. (*See, e.g.*, Ex. 1002 at ¶ 121; Ex. 1006 at 268, Table 11.5 (noting that postprandially, ammonia levels will be 30–60 μmol/L higher depending on time and nitrogen load); Ex. 1012 at 213

(noting diurnal fluctuation of blood ammonia level in UCD patient); Ex. 1017 at 164, Table II (noting effect of protein ingestion on plasma ammonia levels over time); Ex. 1016 at S58; Ex. 1015 at S19.) Given the fluctuation in ammonia levels, and because there is no minimum level of blood ammonia that must be maintained for normal body function, a POSA would have been motivated to monitor plasma ammonia levels and maintain low levels, including levels at or below half the ULN, in order to ensure that the patient's baseline ammonia level is low enough to routinely maintain the patient within normal ranges notwithstanding events that could cause increased ammonia levels, such as the ingestion of food. (Ex. 1002 ¶¶ 29, 36, 143.)

A POSA would have had a reasonable expectation of success in doing so, because it was known that drug dosage could be adjusted to attain a normal or desired plasma ammonia level (which could be, *e.g.*, any level below about 40 μmol/L), the prior art reports patients who achieved plasma levels below half the ULN when taking HPN-100, and HPN-100 was known to be well-tolerated. (Ex. 1007 at [0226], *see also* table following [0201] (subject 1006 has plasma ammonia less than half the ULN, as discussed above at pg. 17–18), [0086], [0203], [0204]; Ex. 1002 ¶ 146).

7. Dependent Claims 5, 8, 11, 14, and 15

Claims 5, 8, and 11 respectively depend from claims 1, 6, and 9, and further require that the glyceryl tri-[4-phenylbutyrate] is administered orally. Claims 14 and 15 depend from claim 12, and further require that the initial effective dose (claim 14) and subsequent effective dose (claim 15) of glyceryl tri-[4-phenylbutyrate] are administered orally. A POSA would have been motivated to administer the drug orally, including because the *'859 Publication* teaches the oral administration of nitrogen scavenging drugs, including glyceryl tri-[4-phenylbutyrate], and oral dosage forms are convenient to administer. (*See, e.g.*, Ex. 1007 at [0002], [0020]–[0021]; Ex. 1002 ¶ 145.)

8. Lack of Secondary Considerations

Although secondary considerations must be taken into account, they do not control the analysis where, as here, there is a strong obviousness case. *See Pfizer, Inc. v. Apotex Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007). Here, no secondary considerations support the nonobviousness of the claims. Patent Owner did not raise any alleged secondary considerations during prosecution of the application that led to the '966 Patent. Further, in its Preliminary Response and Patent Owner Response (Papers 9 and 26) in IPR2016-00829 (which is directed to the grandparent '559 Patent) and its Preliminary Response and Patent Owner Response

(Papers 8 and 25) in IPR2015-01127 (which is directed to the great-grandparent '215 Patent), Patent Owner did not argue any secondary considerations.

In addition, as discussed herein, it was known that increasing the dose of nitrogen scavenging drugs would lower a subject's plasma ammonia level. (*See, e.g.*, Ex. 1007 at [0083].) It was also known to use plasma ammonia levels to guide dosage adjustments of nitrogen scavenging drugs, including glyceryl tri-[4-phenylbutyrate]. (Ex. 1007 at [0083], [0088]–[0092], [0095]–[0099], [0226], [0232]; Ex. 1008 at 8 (recommending individual titration of NaPBA based on therapeutic monitoring).) It was also known that one of the key objectives of nitrogen scavenging therapy was to maintain plasma ammonia levels within normal limits for the subject, and below the ULN. (*See, e.g.*, Ex. 1020 at 3327 ("Laboratory Tests" section, noting that plasma levels of ammonia "should be maintained within normal limits"); Ex. 1007 at [0083], [0046] (noting desire to "maintain a stable level of plasma ammonia," [0074] (noting that plasma ammonia levels less than ULN indicate effective treatment), [0182] (noting that subjects treated with HPN-100 in the disclosed methods will typically "achieve and maintain normal plasma ammonia levels"), [0209] (discussing "superior control of ammonia" and consistent reduction of ammonia levels to below about 40 μmol/L), [0226] (noting that "[d]ietary protein intake or drug dosage or both could be

adjusted to attain a normal or desired plasma ammonia level, e.g. a level below about 40 μmol/L"); Ex. 1002 ¶¶ 120; Ex. 1016 at S58.)

Accordingly claims that more effective ammonia control can be achieved by using plasma ammonia levels in a specific range (*i.e.* those between half the ULN and the ULN) to guide dosage adjustments of glyceryl tri-[4-phenylbutyrate], or by targeting a specific value under the ULN (*i.e.* less than half of the ULN), even if true, would represent merely a difference in degree, not a difference in kind, which is insufficient to change the obviousness calculus here. *See, e.g.*, *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1333–34 (Fed. Cir. 2014) ("The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected.").

Petitioner reserves the right to supplement its positions regarding secondary considerations in response to any allegations raised by Patent Owner.

X. CONCLUSION

For the reasons above, Petitioner respectfully requests institution of IPR for Claims 1-15 of the '966 Patent on the grounds presented.

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 9,326,966 contains 9,374 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: March 27, 2017 By: /Cynthia Lambert Hardman/
Cynthia Lambert Hardman (Reg. No. 53,179)

Certificate of Service

I hereby certify on this 27th day of March 2017, a copy of this Petition for *Inter Partes* Review and the exhibits cited therein have been served by Federal Express on counsel for the patent owner at the correspondence address of record:

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