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.

IPR2017-01159

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,254,278 PURSUANT TO §§ 35 U.S.C. 311-319 AND 37 C.F.R. § 42

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Ex. 1005	Simell, *et al., Waste Nitrogen Excretion Via Amino Acid Acylation: Benzoate and Phenylacetate in Lysinuric Protein Intolerance,* 20 Pediatric Research, 1117-1121 (1986). *("Simell").*
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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. 9,254,278 ("the '278 Patent," Ex. 1001).

The '278 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 '278 Patent was filed.

The '278 Patent discloses purportedly novel methods 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 '278 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 '278 Patent claims. Accordingly, IPR should be instituted and the claims should be cancelled.

II. SUMMARY OF THE '278 PATENT AND ITS PROSECUTION HISTORY

The '278 Patent was filed on August 3, 2015, as a continuation of U.S. Application No. 13/775,000, filed February 22, 2013, now U.S. 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 U.S. Patent No. 8,404,215 (the "'215 patent"). The '278 Patent claims the benefit of U.S. Provisional Application Nos. 61/564,668, filed November 29, 2011, and 61/542,100, filed September 30, 2011. For purposes of this IPR only, Petitioner will assume that the '278 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, 4, 8, and 12, the four independent claims of the '278 Patent, recite:

> 1. A method of treating a subject with a urea cycle disorder, the method comprising:
>
> administering to the subject in need thereof glyceryl tri-[4-phenylbutyrate] in an amount sufficient to produce a fasting plasma ammonia level that is less than half the upper limit of normal for plasma ammonia level.

4. A method for adjusting the dosage of glyceryl tri-[4-phenylbutyrate] in a subject being treated for 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], wherein the adjusted dosage 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, and

wherein the method further comprises restricting the subject's dietary protein intake.

8. A method for adjusting the dosage of glyceryl tri-[4-phenylbutyrate] in a subject being treated for 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], wherein the adjusted dosage 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, and wherein the method further comprises monitoring the subject's ammonia levels if the glyceryl tri-[4-phenylbutyrate] is not being adequately digested by the subject's pancreatic lipases.

12. A method for adjusting the dosage of glyceryl tri-[4-phenylbutyrate] in a subject being treated for a urea cycle disorder who has previously been administered an initial dosage of sodium 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;

(c) administering an initial dosage of glyceryl tri-[4-phenylbutyrate], wherein the initial dosage is determined by the amount of the initial dosage of sodium phenylbutyrate, and

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

(Ex. 1001 at 24:21–26, 24:31–47, 24:56-25:7, 25:17–26:13.)

B. Prosecution History

The prosecution of the ’278 Patent was brief, lasting six months from filing to patent issue. Patent Owner filed the application leading to the ’278 Patent on August 3, 2015, together with an amendment cancelling the eleven original claims and adding three new claims. (Ex. 1001.) On November 3, 2015, the Examiner rejected the claims for nonstatutory double patenting over claims of the grandparent ’215 Patent, parent ’559 Patent, and U.S. Patent No. 8,642,012 (the “’012 Patent”). (Ex. 1022 (Office Action (November 3, 2015)) at 97, 100.) In response, the applicant submitted a terminal disclaimer over these three patents on November 5, 2015. (Ex. 1022 (Response (November 5, 2015)), at 124.) On November 20, 2015, the applicants added twelve additional claims. (Ex. 1022 (Response (November 20, 2015)), at 157-60.) On December 23, 2015, the Examiner allowed the claims. (Ex. 1022 (Notice of Allowance (December 23, 2015)) at 167-69.)

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. (*Id.* 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 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 '278 Patent that 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 '278 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 '278 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 '278 Patent, issued on February 9, 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 Patent and one of its child patents, U.S. Patent No. 9,326,966 (the “’966 Patent”).

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 ’966 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. 1001 at 12:7-8.)

Each of independent claims 1, 4, 8, and 12, as well as dependent claims 5, 9, 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 '278 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. 1001, at 10:28–41.) 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 10:21–27.) 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 4, 8, and 12 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 10:8-13.) 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.

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 1-3 as unpatentable under 35 U.S.C. § 103 as obvious over the *'859 Publication*.

In Ground 2, Petitioner requests IPR and cancellation of claims 4-7 and 12-15 as unpatentable under 35 U.S.C. § 103 as obvious over *Blau*, *Simell*, and the *'859 Publication*.

In Ground 3, Petitioner requests IPR and cancellation of claims 8-11 as unpatentable under 35 U.S.C. § 103 as obvious over *Blau*, *Simell*, the *'859 Publication*, and the *Brusilow '979 Patent*.

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. Ground 1: Claims 1-3 are Unpatentable as Obvious Over the *'859 Publication*

1. Overview of Prior Art Applied in Ground 1

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].)

2. Independent Claim 1

Claim 1 is unpatentable because its subject matter is obvious based on the teachings of the *'859 Publication*, in view of the POSA's knowledge. (Ex. 1002 ¶¶ 60-65.)

Claim 1 is directed to a method of treating a subject with a UCD comprising administering glyceryl tri-[4-phenylbutyrate] in an amount sufficient to produce a fasting plasma ammonia level that is less than half the ULN for plasma ammonia level. (Ex. 1001 at 24:21-26.)

Maintenance of plasma ammonia levels within normal limits is one of the objectives of therapy with nitrogen scavenging drugs. (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 ¶ 78; Ex. 1016 at S58.) There is no minimum level of blood ammonia that must be maintained for normal body function (Ex. 1002 ¶ 29), and keeping ammonia levels low and stable was known to reduce the risk of hyperammonemia. (Ex. 1007 at [0202]; Ex. 1002 ¶ 64.)

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 ¶ 79; 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 sufficient drug to reduce baseline ammonia to levels that would help ensure that the patient routinely stayed within normal plasma ammonia limits notwithstanding events that could cause increased ammonia levels, such as the ingestion of food. (Ex. 1002 at ¶¶ 80, 121.)

The *'859 Publication* discloses a method of treating a subject with a UCD comprising administering glyceryl tri-[4-phenylbutyrate] in an amount sufficient to produce a plasma ammonia level that is less than half the ULN. (Ex. 1002 at ¶¶ 62-63.) Specifically, in the clinical study described in the publication, Patient 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.*; Ex. 1007 at Table under [0201].) This same patient also had an ammonia C_{max} 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. 1002 at ¶ 63; Ex. 1007 at Table under [0201].) When this patient was taking NaPBA, the corresponding ammonia values were much higher (C_{max} of 150 μmol/L, TNAUC of 71.5 μmol/L). (Ex. 1002 at ¶ 63; Ex. 1007 at Table under [0201].) Given the dramatic efficacy of HPN-100 in this patient, and the fact that no patients in the study experienced

serious adverse events with glyceryl tri-[4-phenylbutyrate] (*see* Ex. 1007 at [0203], *see also* [0086]), a POSA would have been motivated to administer the same amount of HPN-100 to other UCD patients. (Ex. 1002 at ¶ 63.)

The *'859 Publication* does not clearly state whether the blood samples obtained in the clinical study were taken in the fasted or fed states. (Ex. 1002 at ¶ 64.) However, as explained above, a POSA would have been motivated to keep a patient's baseline ammonia level low, to keep the patient well-controlled and to reduce the risk of hyperammonemia. (*See supra* pg. 18-19.) Knowing that ammonia levels increase after the ingestion of food, a POSA would have been motivated to keep the fasting plasma ammonia level low, *e.g.* less than half the ULN, to maximize chances of keeping the patient within normal plasma ammonia limits despite transitory spikes in ammonia level. (Ex. 1002 at ¶ 64.) A POSA would have had a reasonable expectation of success of achieving a fasting plasma ammonia level of less than half the ULN, particularly because the *'859 Publication* discloses a dose of HPN-100 that achieved this plasma ammonia level in one of the study patients; HPN-100 was known to be a well-tolerated drug; and because there is no minimum level of blood ammonia that must be maintained for normal body function. (*Id.* at ¶¶ 63-64; Ex. 1007 at Table under [0201], [0203], [0086].)

Accordingly, based on the teachings of the *'859 Publication*, as well as the knowledge of a POSA, claim 1 would have been obvious. (Ex. 1002 ¶¶ 60-65.)

3. Dependent Claims 2 and 3

Claim 2 depends from claim 1, and recites that the ULN for plasma ammonia level is 35 μmol/L. The *'859 Publication* states that "it is recognized in the art that a normal ammonia level will vary depending upon exactly how it is measured." (Ex. 1007 at [0094].) The *'859 Publication* further teaches that the ULN in the clinical study described in the publication varied among the study sites from 26 to 35 μmol/L. (*Id.* at [0201].) Therefore, a POSA reading the *'859 Publication* would have understood that the ULN may vary depending on how it is measured, and that 35 μmol/L would be a reasonable and useful ULN to use. (Ex. 1002 ¶ 67; Ex. 1007 at [0094].)

Claim 3 depends from claim 1, and further requires that "the adjusted dose of glyceryl tri-[4-phenylbutyrate] is 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 administration is a convenient way to administer drugs. (*See, e.g.*, Ex. 1007 at [0002], [0020]–[0021]; Ex. 1002 ¶ 68.)

4. 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 '278 Patent. Further, in its Preliminary Response and Patent Owner Response (Papers 9 and 26) in IPR2016-00829 (which is directed to the parent '559 Patent) and its Preliminary Response and Patent Owner Response (Papers 8 and 25) in IPR2015-01127 (which is directed to the 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 ¶ 78; 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.

B. Ground 2: Claims 4-7 and 12-15 are Unpatentable as Obvious Over *Blau*, *Simell*, and the *'859 Publication*

1. Overview of Prior Art Applied in Ground 2

The *'859 Publication* is reviewed in Section IX.A.1 above.

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) 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).)

2. Motivation to Combine Applied Prior Art

A POSA 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 ¶¶ 70-75.)

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 ¶ 72.) 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 ¶ 72; *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 ¶ 73; Ex. 1007 at Abstract.) Additionally, both the *'859 Publication* and *Simell* provide results of a clinical study using nitrogen scavenging drugs to lower ammonia in patients with UCDs. (Ex. 1004 at Abstract, 1631; Ex. 1007 at Example 3.) By reading both '859 Publication and *Simell*, a POSA would have known the effects of treating patients with nitrogen scavenging drugs. (Ex. 1002 ¶ 74.) A POSA would have been motivated to combine these teachings with *Blau*, as *Blau* provides guidelines on collecting blood to measure ammonia levels. (Ex. 1006 at 273 (Table 11.9); Ex. 1002 ¶ 75.) As the *'859 Publication* and *Simell* both require the collection of blood to measure plasma ammonia levels in order to treat the patients (Ex. 1004 at 1631; Ex. 1007 at [0195]), a POSA would have read *Blau* to understand plasma ammonia measurement guidelines. (Ex. 1002 ¶ 75.)

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 ¶¶ 70-75.)

3. Lack of Secondary Considerations

As discussed above in Section IX.A.4, no secondary considerations support the nonobviousness of the claims.

4. Independent Claim 4

Independent claim 4 would have been obvious based on the teachings of *Blau*, *Simell*, and the *'859 Publication*, in view of the POSA's knowledge. (Ex. 1002 ¶¶ 76-93.)

(a) Preamble

Claim 4 is generally directed to adjusting a dosage of glyceryl tri-[4-phenylbutyrate] in a UCD patient who had previously been administered 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], [0232]; Ex. 1002 ¶ 77.) 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 ¶ 77.)

[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* clearly discloses the use of plasma ammonia levels in adjusting drug dose. (Ex. 1002 at ¶ 77 and n.3.) 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. (*Id.*; Ex. 1007 at [0039], [0226].)

The preamble of independent claim 4 also specifies 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." Maintenance of plasma ammonia levels within normal limits is one of the objectives of therapy with nitrogen scavenging drugs. (Ex. 1002 ¶ 78, citing Ex. 1020 at 3327 ("Laboratory Tests" section, noting that plasma levels of ammonia "should be maintained within normal limits"); Ex. 1007 at [0083] (stating 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."), [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. 1016 at S58 noting that 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").)

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 ¶ 79; 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 ¶ 80.) 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. (*Id.*) 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. (*Id*.)

(b) Claim 4, Part (a)

Part (a) of claim 4 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 ¶ 82.) 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 ¶ 82; *see also* n.4.)

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[3] The '278 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. 1001 at 10:21-29.)

[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 ¶ 82 and n.4. Exhibit 1010, a Lab Update concerning "Measurement of Ammonia in Blood," was published by UMass Memorial Medical Center in Worcester,

Additionally, as evidenced by *Simell*, it was well known in the art before the '278 Patent's priority date to measure fasting blood ammonia levels when treating UCD patients with nitrogen scavenging drugs. (Ex. 1005 at 1118; Ex. 1002 ¶ 83.) *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 ¶ 83.) 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 ¶ 83; Ex. 1005 at 1118; Ex. 1006 at 273 (Table 11.9).)

(c) Claim 4, Part (b)

Part (b) of claim 4 recites "comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level." (Ex. 1001 at 24:39–40.)

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.4.) It also teaches that measurements should be taken at the same time of day and under the same circumstances, due to a diurnal variation in blood ammonia levels. (Ex. 1010; Ex. 1002 at n.4.)

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. 1016 at S58; Ex. 1002 ¶ 78.)

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]; Ex. 1002 ¶ 85.)

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 ¶ 86; 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. (Ex. 1007 at [0083], [0232].) 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 ¶ 86.)

(d) Claim 4, Part (c)

Part (c) of claim 4 recites "administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate], wherein the adjusted dosage 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 Ex. 1007 at [0091], [0092], [0094], [0095]–[0099], [0026];; Ex. 1002 ¶ 88.)

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 ¶¶ 88-89.) 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].)

Again, the goal of nitrogen scavenging therapy for UCD patients is to maintain a stable, normal plasma ammonia level in a subject. (Ex. 1002 at ¶ 78; Ex. 1020 at 3327; Ex. 1007 at [0083], [0226]; Ex. 1016 at S58.) Claim 4 merely recognizes the known premise that increasing the dosage of a nitrogen scavenging

[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.) *See* Ex. 1002 at n. 5. It was also known that the ULN varies depending on how it is measured and depending on the lab that performs the tests. (Ex. 1007 at [0094], [0201].)

drug will decrease plasma ammonia levels. (*See, e.g.*, Ex. 1007 at [0083]; Ex. 1002 ¶ 89.) 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 ¶ 90; 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 ¶ 90.)

(e) Claim 4, Wherein Clause

Claim 4 also recites "wherein the method further comprises restricting the subject's dietary protein intake." It was known that intake of protein can lead to increased ammonia production in UCD patients. (Ex. 1002 at ¶ 92.) For example, *Blau* discloses that, postprandially, ammonia levels will be 30–60 μmol/L higher depending on time and nitrogen load. (Ex. 1006 at 268, Table 11.5). Other prior art references also note the effects of protein intake on ammonia levels. (Ex. 1017

at 164, Table II (noting effect of protein ingestion on plasma ammonia levels over time); Ex. 1016 at S56 (noting that long term treatment of UCD patients involves the use of a low-protein diet, together with nitrogen scavenging drugs and amino acid supplementation).) It was also known that a patient's dietary protein intake could be decreased if feasible to gain further ammonia control. (Ex. 1007 at [0083], [0226]; Ex. 1002 at ¶ 92.) Indeed, per its label, it is required to combine BUPHENYL with dietary protein restriction. (Ex. 1020 at 2.) Accordingly, a POSA would have been motivated to restrict a UCD patient's dietary protein in the course of treating a UCD patient if further ammonia control was needed. (Ex. 1002 at ¶ 92.)

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 4, and would have had a reasonable expectation of success in doing so. (Ex. 1002 at ¶ 93.) 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 method is merely comprised of well-known steps that were routinely practiced by POSAs (Ex. 1002 ¶ 93), and does not specify any particular efficacy measurements. Accordingly, independent claim 4 is unpatentable as obvious. (Ex. 1002 ¶¶ 76-93.)

5. Independent Claim 12

Independent claim 12 would have been obvious based on the teachings of *Blau*, *Simell*, and the *'859 Publication*, in view of the POSA's knowledge. (Ex. 1002 ¶¶ 94-96.)

(a) Preamble

Independent claim 12 is generally directed to a method of adjusting the dosage of glyceryl tri-[4-phenylbutyrate] in a subject who is being treated for a UCD who has previously been administered an initial dosage of NaPBA and who has a fasting plasma ammonia level less than half the ULN.

As discussed above with respect to the preamble of claim 4, 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. (Ex. 1007 at, *e.g.*, [0088]–[0092], [0095]–[0099], [0107]–[0108], [0226], [0232]; Ex. 1002 ¶ 77.) 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 ¶ 77.)

Like the preamble of claim 4, the preamble of claim 12 also specifies 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." As discussed

above with respect to claim 4, 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. (*See supra* Section IX.B.4., incorporated here by reference.)

The preamble of claim 12 also specifies that the subject has previously been administered an initial dosage of NaPBA. It was known that NaPBA and glyceryl tri-[4-phenylbutyrate] are both PAA prodrugs, and that patients could be switched from NaPBA to glyceryl tri-[4-phenylbutyrate]. For example, according to the *'859 Publication*, many patients consider glyceryl tri-[4-phenylbutyrate] a more desirable drug than NaPBA, and experienced better ammonia control with glyceryl tri-[4-phenylbutyrate] than with NaPBA. (Ex. 1007 at [0065], [0046] ("While it is typically necessary to administer smaller doses of sodium PBA 3-6 times per day to maintain a stable level of plasma ammonia, similar results can be achieved with only 2-3 doses of HPN-100 per day."), [0061] ("FIG. 11 shows that HPN-100 did a better job than PBA of managing plasma levels of nitrogen overnight."), Table following [0204] (in a clinical trial, reporting more, and more serious, adverse effects for NaPBA than for HPN-100), [0209].) Accordingly, a POSA reading the *'859 Publication* would have been motivated to transition a patient from NaPBA to glyceryl tri-[4-phenylbutyrate]. (Ex. 1002 at ¶ 95.) A POSA would have known

how to determine the appropriate dosage of glyceryl tri-[4-phenylbutyrate] based on the prior dose of NaPBA, because conversion methods were taught in the art, including in the *'859 Publication*. (*Id.*; Ex. 1007 at [0067], [0195], Example 3.)

(b) Claim 12, Parts (a) and (b)

Parts (a) and (b) of claims 4 and 12 are identical. Each recites "(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." As discussed above with respect to claim 4, these steps were routine in the art, in view of *Blau*, *Simell*, and the *'859 Publication*. *See supra* Section IX.B.4., incorporated herein by reference; *see also* Ex. 1002 at ¶¶ 81-86.

(c) Claim 12, Part (c)

Part (c) of claim 12 recites "administering an initial dosage of glyceryl tri-[4-phenylbutyrate], wherein the initial dosage is determined by the amount of the initial dosage of sodium phenylbutyrate."

As discussed above, it was known that NaPBA and glyceryl tri-[4-phenylbutyrate] are both PAA prodrugs, and that patients could be switched from NaPBA to glyceryl tri-[4-phenylbutyrate]. For example, according to the *'859 Publication*, many patients consider glyceryl tri-[4-phenylbutyrate] a more desirable drug than NaPBA, and methods of calculating the molar equivalent of glyceryl tri-[4-phenylbutyrate] based on the prior dosage of NaPBA were known.

See supra Section IX.B.5.(a). A POSA would have therefore known how to determine the appropriate initial dosage of glyceryl tri-[4-phenylbutyrate] based on the prior dosage of NaPBA. (Ex. 1002 ¶ 95.)

(d) Claim 12, Part (d)

Part (d) of Claim 12 recites "administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate], wherein the adjusted dosage is greater than the initial dosage of glyceryl tri-[4-phenylbutyrate] if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level."

Parts (d) of claim 12 is substantively identical to part (c) of claim 4. Each recites "administering an adjusted dosage of glyceryl tri-[4]-phenylbutyrate], wherein the adjusted dosage is greater than the initial dosage [of glyceryl tri-[4]-phenylbutyrate]] if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level." As discussed above with respect to claim 4, this step was routine in the art, in view of *Blau*, *Simell*, and the *'859 Publication*. *See supra* Section IX.B.4.(d), incorporated herein by reference; *see also* Ex. 1002 at ¶¶ 87-90.

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. (Ex. 1002 ¶ 96.) 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 ¶¶ 94-95.) Accordingly, independent claim 12 is unpatentable as obvious. (*Id*.)

6. Dependent Claims 5 and 13

Claims 5 and 13 respectively depend from claims 4 and 12, and further require repeating the claimed steps (a)-(c) until the subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level.

As discussed above, maintenance of plasma ammonia levels within normal limits is one of the objectives of therapy with nitrogen scavenging drugs. (*See supra* pg. 18; Ex. 1002 ¶ 78.) There is no minimum level of blood ammonia that must be maintained for normal body function. (Ex. 1002 ¶ 29.)

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 ¶ 79; 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, 99.)

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. 16), [0086], [0203], [0204]; Ex. 1002 ¶ 100.)

7. Dependent Claims 6, 7, 14 and 15

Claims 6 and 7 depend from claim 4, and claims 14 and 15 depend from claim 12. These claims further require that either the initial (claims 6 and 14) or the adjusted (claims 7 and 15) dose of glyceryl tri-[4-phenylbutyrate] is

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]. (*See, e.g.*, Ex. 1007 at [0002], [0020]–[0021]; Ex. 1002 ¶ 101.)

C. Ground 3: Claims 8-11 are Unpatentable as Obvious in View *Blau*, *Simell*, the *'859 Publication*, and the *Brusilow '979 Patent*

1. Overview of Prior Art Applied in Ground 3

Blau, *Simell*, and the *'859 Publication* are reviewed in Section IX.A.1 and IX.B.1 above.

United States Patent No. 5,968,979 ("*the Brusilow '979 Patent*," Ex. 1024), entitled "Triglycerides and ethyl esters of phenylalkanoic acid and phenylalkenoic acid useful in treatment of various disorders," relates to compounds, pharmaceutical compositions, and methods for treating several conditions with PAA prodrugs. (Ex. 1024 at Abstract.) It published on October 19, 1999, and is prior art under 35 U.S.C. § 102(b).

The *Brusilow '979 Patent* discloses that certain compounds—triglycerides and ethyl esters of phenylalkanoic or phenylalkenoic acids—provide a more convenient dosage form of drugs for treatment of nitrogen accumulation disorders, cancer, anemia and hemoglobinopathies. (*Id.* at 3:42-46.) HPN-100 is one of the species disclosed in the genus discussed in the *Brusilow '979 Patent*. (*See id.* at 4:3-28; Ex. 1002 ¶ 50.) The *Brusilow '979 Patent* further discloses that pancreatic

lipase hydrolyzes these triglyceride compounds to produce glycerol and phenylalkanoic or phenylalkenoic acids. (*Id.* at 4:65- 5:1.)

2. Motivation to Combine Applied Prior Art

A POSA administering a dosage of a nitrogen scavenging drug before the priority date of the '278 Patent would have been motivated to combine the teachings of *Blau*, *Simell*, the *'859 Publication*, and the *Brusilow '979 Patent* to arrive at the claimed invention. (Ex. 1002 ¶¶ 79–80.) A POSA reading the *'859 Publication* would have been motivated to look to *Blau* and *Simell* for reasons discussed above in Section IX.B.2.

Further, a POSA interested in administering glyceryl tri-[4-phenylbutyrate] as taught in the *'859 Publication* would have looked to the *Brusilow '979 Patent*, which similarly provides information on the dosing and methods of use of HPN-100. (*See, e.g.*, Ex. 1024 at 3:42-45, 4:3-28; Ex. 1002 at ¶ 103.) Additionally, the *Brusilow '979 Patent* adds information on the metabolism of HPN-100, which would have been of interest to a person of ordinary skill in the art who was treating patients with this drug. (*Id.* at 4:65-5:1; Ex. 1002 at ¶ 103.)

Finally, as stated above in Section IX.B.2, the Federal Circuit has explained that motivation to combine can be found in many different forms, including the testimony of an expert witness regarding knowledge of a POSA. *See Allergan*, 726 F.3d at 1292; *Alza Corp.*, 464 F.3d at 1294; Ex. 1002 at ¶¶ 70-75, 103.

3. Lack of Secondary Considerations

As discussed above in Section IX.A.4, no secondary considerations support the nonobviousness of the claims.

4. Independent Claim 8

Independent claim 8 would have been obvious based on the teachings of *Blau*, *Simell*, the *'859 Publication*, and the *Brusilow '979 Patent*. (Ex. 1002 ¶¶ 104-107.)

(a) Preamble and Parts (a)-(c) of Independent Claim 8

The preamble and parts (a)-(c) are identical to the preamble and parts (a)-(c) of claim 4. As discussed above with respect to claim 4, these aspects of claim 12 were routine in the art, in view of *Blau*, *Simell*, and the *'859 Publication*. *See supra* Section IX.B.4., incorporated herein by reference; *see also* Ex. 1002 at ¶¶ 81-90.

(b) Wherein Clause of Claim 8

Claim 8 further recites "wherein the method further comprises monitoring the subject's ammonia levels if the glyceryl tri-[4-phenylbutyrate] is not being adequately digested by the subject's pancreatic lipases."

It was known that glyceryl tri-[4-phenylbutyrate] is hydrolyzed by human pancreatic lipases, which release PBA from the glyceryl tri-[4-phenylbutyrate] prodrug. (Ex. 1024 at 4:65-5:1.) Accordingly, as Dr. Vaux states, a POSA would have been motivated to monitor the subject's ammonia levels if the glyceryl tri-[4-

phenylbutyrate] was not being adequately digested by the subject's pancreatic lipases, because in such a case, the POSA would have known that PBA was not being made available in the body to convert to PAA and scavenge nitrogen. (Ex. 1002 at ¶ 106.) Moreover, as Dr. Vaux states, a POSA would have been motivated to monitor a subject's plasma ammonia levels for other reasons as well (e.g. to determine the efficacy of the drug regimen, *see, e.g.*, *'859 Publication* at [0226], and thus would have been carrying out this step regardless of whether the glyceryl tri-[4-phenylbutyrate] was being adequately digested by the subject's pancreatic lipases. (Ex. 1002 at ¶ 106.)

Based on the teachings of *Blau*, *Simell*, the *'859 Publication*, and the *Brusilow '979 Patent*, as well as the knowledge of a POSA, a POSA would have been motivated to carry out the method of claim 8, and would have had a reasonable expectation of success in doing so. (Ex. 1002 at ¶ 106.) "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. Accordingly, independent claim 8 is unpatentable as obvious. (Ex. 1002 ¶¶ 104-107.)

5. Dependent Claim 9

Claim 9 depends from claim 8 and further requires repeating the claimed steps (a)-(c) until the subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal for plasma ammonia level. The addition limitations recited in claim 9 are identical to those of claims 5 and 13, and would have been obvious in view of *Blau*, *Simell*, the *'859 Publication*, and the *Brusilow '979 Patent* for the same reasons discussed above. *See supra* Section IX.B.6., incorporated herein by reference; *see also* Ex. 1002 at ¶ 108.

6. Dependent Claims 10 and 11

Claims 10 and 11 depend from claim 8, and require respectively that the initial or the adjusted dose of glyceryl tri-[4-phenylbutyrate] is 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]. (*See, e.g.*, Ex. 1007 at [0002], [0020]–[0021]; Ex. 1002 ¶ 110.)

X. CONCLUSION

For the reasons above, Petitioner respectfully requests institution of IPR for Claims 1-15 of the ’278 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. 9,254,278 contains 10,761 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 27th, 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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