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, INC.

Patent Owner.

IPR2016-00829

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,095,559 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. 9,095,559 ("the '559 patent," Ex. 1001).

II. OVERVIEW

A. Summary of the '559 Patent

The '559 patent is directed to methods of administering and adjusting the dosage of tri-[4-phenylbutyrate], a nitrogen scavenging drug, based on the fasting plasma ammonia level of a subject. Nitrogen scavenging drugs, and their use in reducing plasma ammonia levels in patients with nitrogen retention disorders, were well known long before the '559 patent was filed. The use of the nitrogen scavenging drugs glyceryl tri-[4-phenyl-butyrate] (also known as "HPN-100"), phenylbutyric acid ("PBA"), sodium phenylbutyrate ("NaPBA"), sodium benzoate, and combinations thereof, to treat patients with urea cycle disorders ("UCDs") and hepatic encephalopathy, was specifically disclosed in the prior art.

The '559 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 maintain normal levels has been done for decades.

As shown below, the claims of the '559 patent 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 ("**priority date**") of the '559 patent. Accordingly, IPR should be instituted.

B. Summary of the Prosecution History of the '559 Patent

The application leading to the '559 patent was filed on February 22, 2013.[1] (Ex. 1001.) The Examiner issued a non-final rejection on January 9, 2015, rejecting the claims for nonstatutory double patenting. (Ex. 1022 at 295–98.) In

[1] The '559 patent was filed on February 22, 2013, as a divisional of U.S. Application No. 13/417,137, filed March 9, 2012, now Patent No. 8,404,215 (the "'215 patent"). The '559 patent claims the benefit of U.S. Provisional Application No. 61/564,668, filed on November 29, 2011, and U.S. Provisional Application No. 61/542,100, filed September 30, 2011. The '559 patent is assigned to Horizon Therapeutics, Inc. ("Horizon" or "Patent Owner"). For purposes of this IPR only, Petitioner will assume that the '559 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.

response, the applicant submitted a terminal disclaimer. (Ex. 1022 at 325.) The Examiner then issued a Notice of Allowance on May 20, 2015, stating the following reasons for allowance:

> Following a diligent search it was determined that the prior art neither teaches nor provides adequate motivation to arrive at the instantly claimed method 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-phenyl-butyrate], 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-phenyl-butyrate], wherein the adjusted dosage is greater than the initial dosage if the fasting blood ammonia level is greater than half the upper limit of normal for plasma ammonia level.

(Ex. 1022 at 349–50.)

On June 5, 2015, the applicant submitted a Request for Continued Examination, and amended the claims to specify that "the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level and less than the upper limit of normal for plasma ammonia level or that the subject

with a urea cycle disorder has previously been administered an initial dosage of glyceryl tri-[4-phenyl-butyrate] and has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level." (Ex. 1023 at 484–485.) The applicant also added new dependent claims, specifying the oral administration of glyceryl tri-[4-phenyl-butyrate].

The Examiner then issued a Notice of Allowance on June 18, 2015, repeating the same reasons for allowance quoted above. (Ex. 1023 at 498–99.)

As shown below, the claimed subject matter that the Examiner believed was absent from the prior art was in fact well known.

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. (Ex. 1002 at ¶ 30.) 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 ¶ 30.) 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 parent '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 '559 patent that treatment options for UCDs included the use of nitrogen scavenging drugs such as sodium benzoate, PBA, HPN-100, and NaPBA. (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. 1002 ¶ 33; Ex. 1020 at 3327.)

In vivo, NaPB rapidly oxidizes to form one molecule of phenylacetic acid ("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 ¶ 34.) Each molecule of PAGN carries away two molecules of nitrogen. (Ex. 1007 at [0023]; Ex. 1002 ¶ 34.) Glyceryl tri-[4-phenylbutyrate] is hydrolyzed to release three molecules of phenylbutyrate, which in turn are oxidized to form three molecules of PAA and, in turn, three molecules of PAGN. 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 '559 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 ¶ 32.) One 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 ¶¶ 29, 33, 35–41, 48; Ex. 1007 at, *e.g.*, [0083]; 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.)

It was also well known before the priority date of the '559 patent that an effective dosage of a PAA prodrug could be determined by taking into account the conversion of PAA prodrugs to urinary PAGN, which was reported in the prior art to be 60–75%. (Ex. 1002 ¶ 36; Ex. 1007 at [0020], [0043], [0223].) Therefore, the '559 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 '559 patent, issued on August 4, 2015, 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. 504494.

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 January 13, 2016 and January 14, 2016, Horizon served Lupin Pharmaceuticals, Inc. and Lupin Ltd., respectively, with a complaint in the District Court for the District of New Jersey (Case No. 1:15-cv-07624) alleging that Petitioner is infringing the '559 patent, the parent '215 patent, and Horizon's U.S. Patent 8,642,012.

The parent '215 patent is the subject of IPR2015-01127, filed by Par Pharmaceutical, Inc., which has been instituted. Lupin filed IPR2016-00284 against the '215 patent, together with a motion for joinder with IPR2015-01127. Lupin's IPR is pending a decision on institution and joinder.

Par and Lupin also filed IPR2015-01117 and IPR2016-00283, respectively, against Horizon's U.S. Patent 8,642,012, although that patent is not related to the '559 patent.

Horizon is also asserting the parent '215 patent and U.S. Patent 8,642,012 against Par in the Eastern District of Texas (Case No. 2-14-cv-00384).

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). Ms. Holland's email address is eholland@goodwinprocter.com, and Ms. Hardman's email address is chardman@goodwinprocter.com.

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

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). With respect to the '559 patent, Petitioner submits that a POSA is a physician with an M.D. degree, with a residency in pediatrics or internal medicine, and specialized training in the diagnosis or treatment of inherited metabolic disorders, such as UCD 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

A. Broadest Reasonable Interpretation Standard

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretation in light of the specification of the '559 patent. The Patent Trial and Appeal Board ("Board") interprets claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48766 (Aug. 14, 2012).

Under this standard, claim terms are generally given their ordinary and customary meaning, as would be understood by a POSA in the context of the entire disclosure. *See In re Translogic Tech., Inc.* 504 F.3d 1249, 1257 (Fed. Cir. 2007). If a special definition for a claim term is proffered, it must be described in the specification "with reasonable clarity, deliberateness, and precision." *In re Paulsen,* 30 F.3d 1475, 1480 (Fed. Cir. 1994). Absent such a special definition, limitations are not to be read from the specification into the claims. *See In re Van Guens,* 988 F.2d 1181, 1184 (Fed. Cir. 1993).

B. Claim Construction for the '559 Patent

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 12:11–12.)

Each of independent claims 1, 2, and 3, as well as dependent claims 5, 6, and 8, 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 '559 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 10:30–44.) 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, 2, and 6 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 10:20–25.) 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.

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 *inter partes* review and cancellation of claims 1, 2, 4, 5, 7-10, 12, and 13 as unpatentable under 35 U.S.C. § 103 as obvious over *Blau*, *Simell*, and the *'859 Publication*.

In Ground 2, Petitioner requests *inter partes* review and cancellation of claims 3, 6, 11, 14, and 15 as unpatentable under 35 U.S.C. § 103 as obvious over *Blau*, *Simell*, the *'859 Publication*, and *Brusilow '84*.

Petitioner provides the declaration of Keith Vaux, M.D. in support of the grounds for challenging the claims. (Ex. 1002.) Dr. Vaux is an expert in the field. (Ex. 1002 ¶¶ 1–4; Ex. 1003.)

Claims 1–3, the three independent claims of the '559 patent, recite:

> 1. 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.

2. 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.

3. A method of administering glyceryl tri-[4-phenylbutyrate] to a subject having a urea cycle disorder, the method comprising:

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

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

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

(Ex. 1001 at 24:21–60.)

A. Ground 1: Claims 1, 2, 4, 5, 7-10, 12, and 13 Are Unpatentable as Obvious Over *Blau*, *Simell*, and the *'859 Publication*

1. Overview of Prior Art Applied in Ground 1

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, a type of UCD, following the standardized induction of hyperammonemia. (Ex. 1002 ¶ 45; 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. *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 ¶ 46.) *Blau* discusses different types of UCDs and laboratory tests that should be performed when treating a UCD patient.[2] (Ex. 1006 at 261, 270–71, 273 (Table 11.9).)

[2] 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. Exhibit 1010, a Lab Update concerning "Measurement of Ammonia in Blood," was published by UMass Memorial Medical Center in Worcester, Massachusetts, in February 2007, and is available at https://www.ummlabs.org/ClientNews.asp. UMass Memorial's "Lab Updates" are publicly-available announcements regarding clinical tests, procedures, and results. *See* http://www.umassmemoriallabs.org/test-resources/updates. 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

The *'859 Publication* is the publication for U.S. Patent No. 8,642,012, which is also assigned to Horizon. (Ex. 1007.) It was published on January 14, 2010, and qualifies as prior art under 35 U.S.C. § 102(b). It teaches methods of adjusting the dose of a nitrogen scavenging drug, including the drugs sodium phenylbutyrate and glyceryl tri-[4-phenylbutyrate], in subjects with UCDs who had previously been administered a dosage of the nitrogen scavenging drug, based in part on evaluating plasma ammonia levels. (Ex. 1007 at [0020]–[0022], Example 3, [0088]–[0091], [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].) Either or each of these parameters can be monitored to assess the dosage of drug. (*Id.* at [0091].)

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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 n. 4.)

To determine whether the plasma ammonia levels are acceptable, the *'859 Publication* teaches comparing a plasma ammonia level to the ULN of plasma ammonia for the subject, and defines that ULN as about 35 or 40 μmol/L. (*See id.* at [0063], Fig. 13, [0094], [0201].) It also discloses that the plasma ammonia level can help assess the effectiveness of the overall drug and dietary regimen for a particular patient. (*Id.* at [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 ¶ 43.)

The *'859 Publication* teaches treating a UCD patient with a PAA prodrug, such as HPN-100 or NaPBA. (Ex. 1007 at [0144]–[0156], [0221]–[0229].) HPN-100 is a preferred embodiment. (*Id.* at [0036].) It is described as providing better control of ammonia levels than NaPBA in a clinical study of UCD patients. (*Id.* at [0060], [0137], [0202]–[0203], [0209], Figs. 12, 13.)

The *'859 Publication* further teaches that when HPN-100 or NaPBA is administered to a patient, it is converted to urinary PAGN at a rate of 60–75%. (Ex. 1007 at [0020], [0043], [0223].) The *'859 Publication* teaches using this known conversion rate to determine an effective dose of the PAA prodrug to administer. (Ex. 1007 at [0221]–[0229].) The *'859 Publication* explains that after the PAA prodrug is administered, the urinary PAGN excretion may be measured. (Ex. 1007 at [0224].)

2. Motivation to Combine Applied Prior Art

A POSA administering or adjusting the dosage of a nitrogen scavenging drug in a patient with a nitrogen retention disorder 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 ¶¶ 47–51.)

Simell discusses methods of administering nitrogen scavenging drugs, specifically sodium benzoate, phenylacetate, and phenylbutyrate, to lower blood ammonia levels in UCD patients. (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 ¶ 49.) 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 ¶ 49; *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 ¶ 50; 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 such drugs in some UCD patients, and would have additionally referred to *Blau* for guidance on measuring fasting blood ammonia levels. (Ex. 1002 ¶¶ 49–50, 59, 67.)

3. 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 '559 patent. Further, in its Preliminary Response and Patent Owner Response (Papers 8 and 25) in IPR2015-01127 (which is directed to the parent '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 fasting 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 [0088]–[0091], [0095]–[0099], [0226], [0232]; Ex. 1008 at 8 (recommending individual titration of NaPB 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. (*See, e.g.*, Ex. 1020 at 3327 ("Laboratory Tests" section); Ex. 1007 at [0083]; Ex. 1016 at S58; Ex. 1002 at ¶ 51.) Accordingly a claim 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], even if true, would be 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.

4. Independent Claims 1 and 2

Independent claims 1 and 2 would have been obvious based on the teachings of *Blau*, *Simell*, and the *'859 Publication*, in view of the POSA's knowledge. (Ex. 1002 ¶¶ 52–66.)

(a) Preambles of Independent Claims 1 and 2

Independent claims 1 and 2 are generally directed to adjusting a dosage of glyceryl tri-[4-phenylbutyrate] that had previously been administered to a subject by taking into account the subject's plasma ammonia levels. (Ex. 1001 at 24:28–31, 24:48–50.)

The *'859 Publication* teaches methods of administering nitrogen scavenging drugs such as glyceryl tri-[4-phenylbutyrate] to UCD patients, including methods based on taking into account the patient's plasma ammonia level. (Ex. 1007 at, *e.g.*, [0088]–[0091], [0095]–[0099], [0107]–[0108], [0226], [0232]; Ex. 1002 ¶

53.) The *'859 Publication* makes clear that the dosage of such drugs can be adjusted based in part on plasma ammonia values. 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 ¶ 53.) The *'859 Publication* provides methods of monitoring the effectiveness of the treatment of a UCD patient with glyceryl tri-[4-phenylbutyrate], and of adjusting doses of the drug, that involve measuring ammonia and ensuring adequate ammonia control. (Ex. 1007 at [0088]–[0091], [0095]–[0099], [0226], [0232]; Ex. 1002 ¶ 53.)[3]

[3] 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 is a "teaching away" from the claimed subject matter. (*See, e.g.*, Ex. 1007 at [0073], [0099], [0020].) The *'859 Publication* clearly discloses the use of plasma ammonia levels in adjusting drug dose. (Ex. 1002 at ¶ 53.) 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 ¶ 56.)

The preambles of independent claims 1 and 2 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. 1001 at 24:28–31, 24:48–50.) 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); Ex. 1007 at [0083]; Ex. 1016 at S58; Ex. 1002 ¶ 54.) 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 ¶¶ 49, 55; 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 ¶¶ 51, 55.) 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 ¶¶ 51, 55.) 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 ¶¶ 51, 55.)

(b) Part (a) of Independent Claims 1 and 2

Part (a) of claims 1 and 2 recites "measuring a fasting plasma ammonia level for the subject." (Ex. 1001 at 24:32, 51.)

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.[4] (Ex. 1006 at 273 (Table 11.9); Ex. 1002 ¶ 58.) 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. (Ex. 1002 ¶ 58; *see also* n.2.)

Additionally, as evidenced by *Simell*, it was well known in the art before the '559 patent's priority date to measure fasting blood ammonia levels when treating

[4] The '559 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 10:25–31.)

UCD patients with nitrogen scavenging drugs. (Ex. 1005 at 1118; Ex. 1002 ¶ 59.) *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 ¶ 59.) 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 ¶¶ 49, 59; Ex. 1005 at 1118; Ex. 1006 at 273 (Table 11.9).)

(c) Part (b) of Independent Claims 1 and 2

Part (b) of claims 1 and 2 recites "comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level." (Ex. 1001 at 24:33–34, 52–53.)

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); Ex. 1007 at [0083]; Ex. 1016 at S58; Ex. 1002 ¶ 61.) 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 ¶ 61; 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 ¶ 61.) 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 ¶ 61.)

(d) Part (c) of Independent Claims 1 and 2

Part (c) of claim 1 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." (Ex. 1001 at 24:35–39.) Part (c) of claim 2 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." (Ex. 1001 at 24:54–57.)

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]; [0094]; [0095]–[0099]; Ex. 1002 ¶ 63.) Specifically, the *'859 Publication* states that if ammonia control is inadequate, the dosage of the nitrogen scavenging drug may be increased. (Ex. at [0083]; Ex. 1002 ¶ 63.)

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 ¶ 64.) 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 ¶ 64.)

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 ¶ 71;

[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. 4.

Ex. 1020 at 3327 ("Laboratory Tests" section); Ex. 1007 at [0083]; Ex. 1016 at S58.) Claims 1 and 2 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 ¶ 65.) 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 ¶ 65; 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 ¶ 65.)

Accordingly, based on the teachings of *Blau*, *Simell*, and the *'859 Publication*, as well as the knowledge of a POSA, independent claims 1 and 2 would have been obvious. (Ex. 1002 ¶ 66.)

5. Dependent Claim 4

Dependent claim 4 recites "[t]he method of claim 1 or 2, wherein administering the adjusted dosage of glyceryl tri[4-phenylbutyrate] produces a normal average daily ammonia level in the subject." (Ex. 1001 at 25:6–8.) Dependent claim 4 would have been obvious to a POSA in view of *Blau*, *Simell*, and the *'859 Publication.* (Ex. 1002 ¶ 67.)

It was well known to administer nitrogen scavenging drugs, including glyceryl tri-[4-phenylbutyrate], to lower plasma ammonia levels. (*See, e.g.*, Ex. 1005 at Abstract, 1117–18; Ex. 1007 at [0021]–[0023].) And maintenance of plasma ammonia levels within normal limits is one of the objectives of therapy with nitrogen scavenging drugs. (Ex. 1002 ¶ 67; Ex. 1020 at 3327 ("Laboratory Tests" section); Ex. 1007 at [0083]; Ex. 1016 at S58.) Accordingly a POSA would have been motivated to monitor plasma ammonia levels and administer an increased dose of glyceryl tri-[4-phenylbutyrate] as needed to achieve good ammonia control and normal average daily ammonia levels, as was achieved, for example, in the population in Figure 13 of the *'859 Publication* with HPN-100 treatment. (Ex. 1002 ¶ 67; Ex. 1007 at [0083], [0094], [0137], Fig. 13.)

6. Dependent Claim 5

Claim 5 depends from claim 4 and further requires repeating the claimed steps until the subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal 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. (Ex. 1002 ¶ 74; Ex. 1020 at 3327 ("Laboratory Tests" section); Ex. 1007 at [0083]; Ex. 1016 at S58.) There is no minimum level of blood ammonia that must be maintained for normal body function. (Ex. 1002 ¶ 68.) 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 ¶ 68; 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, a POSA would have been motivated to monitor plasma ammonia levels and maintain the 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 ¶ 68.)

7. Dependent Claim 7

Dependent claim 7 depends from any of claims 1-3, 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 a ULN in certain clinical tests was between 26 and 35 μmol/L. (*Id.*)

Therefore, a POSA reading the *'859 Publication* would have understood that the ULN may vary depending on how it is measured, and it was known before the priority date of the '559 patent that a ULN plasma ammonia level may be 35 μmol/L. (Ex. 1002 ¶ 69; Ex. 1007 at [0094].)

8. Dependent Claim 8

Claim 8 depends from any of claims 1-3, and specifies that the ULN is specific to the laboratory in which the fasting plasma ammonia level is measured. It was known in the art that a normal ammonia level will vary depending upon exactly how it is measured, and thus a POSA would have been motivated to use an ULN that is specific to the laboratory in which the fasting plasma ammonia level is measured in order to have consistency between the ULN and the patient's results. (Ex. 1002 ¶ 70; Ex. 1007 at [0094], [0201] (noting that in a clinical study, the ULN varied among study sites).)

9. Dependent Claim 9

Dependent claim 9 depends from any of claims 1–3, and recites "[t]he method of any of claims 1–3" with the additional step of "determining an upper limit of normal for plasma ammonia level for the subject prior to step (b)." (Ex. 1001 at 25:6–8.) The *'859 Publication* indicates that "plasma levels of ammonia are acceptable when they are at or below a level considered normal for the subject, and commonly this would mean plasma ammonia level is below about 40 μmol/L." (Ex. 1007 at [0094].) The *'859 Publication* further states that "[I]t is recognized in the art that a normal ammonia level will vary depending upon exactly how it is measured." (*Id.*) It was also known that the ULN varies by patient, based on, *e.g.*, age.[6] Accordingly a POSA would have been motivated to determine an ULN for a given subject, prior to comparing a given measurement from a subject to an ULN. (Ex. 1002 ¶ 71.)

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[6] 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, n.6.

Accordingly, based on the teachings of *Blau*, *Simell*, and the *'859 Publication*, as well as the knowledge of a POSA, dependent claim 9 would have been obvious. (Ex. 1002 ¶ 71.)

10. Dependent Claim 10

Dependent claim 10 depends from claim 1 or 2, and recites "the method of claim 1 or 2, wherein the adjusted dosage is calculated by: (i) measuring urinary phenylacetyl glutamine (P AGN) output; and (ii) calculating an effective adjusted dosage of glyceryl tri-[4-phenylbutyrate] based on the urinary PAGN output, wherein the effective adjusted dosage is calculated based on a mean conversion of glyceryl tri-[4-phenylbutyrate] to urinary PAGN of 60 to 75%."

The *'859 Publication* teaches that glyceryl tri-[4-phenylbutyrate] has a conversion rate of 60–75% into urinary PAGN. (Ex. 1002 ¶ 78; Ex. 1007 at [0020], [0043], [0223].) The *'859 Publication* further teaches that this conversion rate may be used to determine an effective dose of glyceryl tri-[4-phenylbutyrate] to administer. (Ex. 1007 at [0144]–[0156], [0221]–[0223].) A POSA would have further understood that after administering glyceryl tri-[4-phenylbutyrate], the patient's urinary PAGN excretion may be measured to determine whether the dose should be adjusted. (Ex. 1002 ¶ 71; Ex. 1007 at [0224].)

Accordingly, based on the teachings of *Blau*, *Simell*, and the *'859 Publication*, as well as the knowledge of a POSA, dependent claim 10 would have been obvious. (Ex. 1002 ¶ 71.)

11. Dependent Claims 12 and 13

Claims 12 and 13 respectively depend on claims 1 and 2, and further require that the 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 ¶ 73.)

B. Ground 2: Claims 3, 6, 11, 14, and 15 are Unpatentable as Obvious in View of *Blau*, *Simell*, the *'859 Publication*, and *Brusilow '84*

1. Overview of Prior Art Applied in Ground 2

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

Brusilow '84 (Ex. 1004) was published in 1984, and is prior art to the '559 claims under 35 U.S.C. § 102(b). It describes methods of treating episodic hyperammonemia in seven children with UCDs. (Ex. 1002 ¶ 77; Ex. 1004 at Abstract, 1630–31.) *Brusilow '84* discloses measuring a plasma ammonium level for a subject who was anorexic for twenty-four hours, comparing that measured

plasma ammonium level to an ULN for plasma ammonium level, and then administering a dosage of the nitrogen scavenging drugs sodium benzoate and sodium phenylacetate where the measured plasma ammonium level was greater than half the ULN for blood ammonium level. (Ex. 1004 at 1631; Ex. 1002 ¶ 77.)

Brusilow '84 shows that monitoring a patient's plasma ammonia levels, comparing those levels to normal limits for plasma ammonia, and using the results of that comparison to guide treatment decisions has long been a standard approach to treating UCD patients. (Ex. 1002 ¶ 77.) Specifically, with respect to a 12-month-old UCD patient, prior to commencement of drug treatment, the boy's plasma ammonium level was measured at 145 μM. (Ex. 1004 at 1631.) *Brusilow '84* teaches that normal plasma ammonium levels are less than 35 μM (ULN is therefore 35 μM). (Ex. 1004 at 1631, 1632 at Fig. 1; Ex. 1002 ¶ 77.) The boy had a plasma ammonia level above normal, and was therefore treated with sodium benzoate and PAA (each in a dose of 250 mg/kg) over one hour. (*Id*. at 1631.) Three hours after the infusion was completed his ammonium level had decreased, but at 79 μM, it was still more than half of the upper limit of normal. (*Id*. at 1631, 1632 at Fig. 1.) Accordingly treatment with nitrogen scavenging drugs continued, this time with sodium benzoate (500 mg/kg) in three divided doses over six hours. (*Id*.) After 19 hours of therapy, the plasma ammonium level was within normal limits, at 33 μM. (*Id*.)

2. Motivation to Combine Prior Art Applied in Ground 2

A POSA administering a dosage of a nitrogen scavenging drug before the priority date of the '559 patent would have been motivated to combine the teachings of *Blau*, *Simell*, the *'859 Publication*, and *Brusilow '84* 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 stated above in Section IX.A.2.

Additionally, a POSA reading *Brusilow '84* would have been motivated to look to *Simell* because both provide results of a clinical study using nitrogen scavenging drugs to treat patients with UCDs. (Ex. 1002 ¶ 79; Ex. 1004 at Abstract, 1631; Ex. 1005 at Abstract, 1117–18.) By reading both *Brusilow '84* and *Simell*, a POSA would have known the effects of treating a UCD patient with nitrogen scavenging drugs. (Ex. 1002 ¶ 79.)

A POSA would have been motivated to combine these teachings with *Blau*, as *Blau* provides guidelines on collecting blood to measure ammonia levels. (Ex. 1002 ¶ 80; Ex. 1006 at 273 (Table 11.9).) As *Brusilow '84* and *Simell* both require the collection of blood to measure blood ammonia levels in order to treat the patients (Ex. 1004 at 1631; Ex. 1005 at 1118), a POSA would have read *Blau* to understand blood ammonia measurement guidelines. (Ex. 1002 ¶ 80.)

Finally, as stated above in Section IX.A.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.

3. Lack of Secondary Considerations

As discussed above in Section IX.A.3, no secondary considerations support the nonobviousness of the claims.

4. Independent Claim 3

Independent claim 3 would have been obvious based on the teachings of *Blau*, *Simell*, the *'859 Publication*, and *Brusilow '84*. (Ex. 1002 ¶¶ 81–94.)

(a) Preamble of Independent Claim 3

Independent claim 3 is generally directed to a method of administering an initial dose of glyceryl tri-[4-phenylbutyrate] to a subject having a UCD by taking into account the subject's plasma ammonia levels. (Ex. 1001 at 24:28–31, 24:48–50.) This subject matter was taught in the prior art.

Among other things, the *'859 Publication* explicitly teaches methods of administering the nitrogen scavenging drug glyceryl tri-[4-phenylbutyrate] to UCD patients, including methods that include taking into account the patient's plasma ammonia level. (Ex. 1007 at, *e.g.*, [0088]–[0091], [0095]–[0099], [0107]–[0108], [0226], [0232]; Ex. 1002 at ¶ 82.)

Brusilow '84 discloses treatment of episodic hyperammonemia in UCD patients with the nitrogen scavenging drugs sodium benzoate and sodium phenylacetate. (Ex. 1004 at 1630; Ex. 1002 at ¶ 83.) Drug therapy was initiated when the patients presented with plasma ammonia levels above the ULN. (*Id.* at 1631; Ex. 1002 at ¶ 83.)

(b) Part (a) of Independent Claim 3

Part (a) of claim 3 recites "measuring a first fasting plasma ammonia level for the subject." (Ex. 1001 at 24:52–53.)

The *'859 Publication* discloses measuring plasma ammonia levels as part of methods of treating UCD patients with glyceryl tri-[4-phenylbutyrate]. (*Id.* [0088]–[0091], [0095]–[0099], [0023].)

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.[7] (Ex. 1006 at 273 (Table 11.9).) 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,

[7] The '559 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 10:34–35, 39–40.)

which would provide a fasting blood ammonia level. (Ex. 1002 ¶ 86; *see also id.* at n.2.)

Additionally, as evidenced by *Simell*, it was well known in the art before the '559 patent's priority date to measure fasting blood ammonia levels when administering nitrogen scavenging drugs to UCD patients. (Ex. 1005 at 1118; Ex. 1002 at ¶ 87.) *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 drugs. (Ex. 1005 at 1118, Fig. 1; Ex. 1002 at ¶ 87.) In addition, *Brusilow '84* discloses measuring a child's plasma ammonium level after he had been anorexic for 24 hours, which means in this context that he had not eaten in 24 hours. (Ex. 1004 at 1631; Ex. 1002 ¶ 87.) Therefore, a POSA reading the *'859 Publication* in view of *Blau*, *Simell*, and *Brusilow '84* would have understood the need to measure a fasting plasma ammonia level. (Ex. 1002 ¶ 95; Ex. 1005 at 1118; Ex. 1006 at 273 (Table 11.9).)

(c) Part (b) of Independent Claim 3

Part (b) of claim 3 recites "comparing the first fasting plasma ammonia level to the upper limit of normal for plasma ammonia level." (Ex. 1001 at 24:54–55.)

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); Ex. 1007 at [0083]; Ex. 1016 at S58; Ex. 1002 at ¶

97.) *Brusilow '84* discloses measuring a patient's fasting plasma ammonium level and comparing this value to a normal plasma ammonium value, which was less than 35 μM (ULN is therefore 35 μM). (Ex. 1004 at 1631, 1632 (Fig. 1); Ex. 1002 at ¶ 89.) *Brusilow '84* then describes treating the patient with the nitrogen scavenging drugs sodium benzoate and phenylacetate after comparing the measured fasting plasma ammonium value to the ULN. (Ex. 1004 at 1631, 1632 (Fig. 1).)

In addition, 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 ¶ 90; 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 ¶ 90.) 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 ¶ 90.)

(d) Part (c) of Independent Claim 3

Part (c) of claim 3 recites "administering an initial dosage of glyceryl tri-[4-phenylbutyrate] to the subject if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level and less than the upper limit of normal for plasma ammonia level." (Ex. 1001 at 24:35–39.)

It was well known to administer nitrogen scavenging drugs, including glyceryl tri-[4-phenylbutyrate], to lower plasma ammonia levels. For example, the *'859 Publication* provides methods of treating UCD patients with glyceryl tri-[4-phenylbutyrate] that involve measuring the patient's plasma ammonia levels. (*Id.* at [0088]–[0091], [0095]–[0099], [0023]; Ex. 1002 at ¶ 92.) Similarly, *Brusilow '84* teaches administering a nitrogen scavenging drug in response to elevated fasting plasma ammonia levels. (Ex. 1004 at 1631; Ex. 1002 at ¶ 92.)

A POSA reading the *'859 Publication* in view of *Blau*, *Simell*, and *Brusilow '84* would have administered a dose of glyceryl tri-[4-phenylbutyrate] to a subject if the measured fasting plasma ammonia level was greater than half the ULN but less than the ULN. (Ex. 1002 ¶ 93.) The goal of nitrogen scavenging therapy for UCD patients is to maintain a stable, normal plasma ammonia level in a subject, and it was well-known that nitrogen scavenging drugs (including glyceryl tri-[4-

phenylbutyrate]) could be used to lower plasma ammonia levels. (Ex. 1002 at ¶ 93; Ex. 1020 at 3327; Ex. 1007 at [0083], [0226], [0232].) Claim 3 merely recognizes the known premise that administering a nitrogen scavenging drug will decrease plasma ammonia levels. (Ex. 1007 at [0083].) 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 ¶ 93; 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 ¶ 93.)

Accordingly, based on the teachings of *Blau*, *Simell*, the *'859 Publication*, and *Brusilow '84*, as well as the knowledge of a POSA, independent claim 3 would have been obvious. (Ex. 1002 ¶ 94.)

5. Dependent Claim 6

Claim 6 depends from claim 3, and further requires measuring a second fasting plasma ammonia level for the subject; comparing it to the ULN; and administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate] that is greater than the initial dosage if the second fasting plasma ammonia level is greater than half the ULN and less than the ULN. As previously discussed, a POSA would have known that ammonia levels vary throughout the day and in response to ingestion of protein (which can vary from day to day). (Ex. 1002 ¶ 95; *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. 1016 at S58; Ex. 1015 at S19.) Therefore, for similar reasons as discussed above for claim 3, it would have been obvious to take a second measurement of a patient's fasting plasma ammonia to determine whether the dosage of glyceryl tri-[4-phenylbutyrate] would need to be adjusted to maintain the patient's ammonia level below the ULN. (Ex. 1002 ¶ 95.)

6. Dependent Claim 11

Claim 11 depends from claim 3, and recites "the method of claim 3, wherein the initial dosage is calculated by: (i) determining a target urinary phenylacetyl

glutamine (P AGN) output; and (ii) calculating an effective initial dosage of glyceryl tri-[4-phenylbutyrate] based on a mean conversion of glyceryl tri-[4-phenylbutyrate] to urinary PAGN of 60 to 75%."

The *'859 Publication* teaches that glyceryl tri-[4-phenylbutyrate] has a conversion rate of 60–75% into urinary PAGN. (Ex. 1002 ¶ 97; Ex. 1007 at [0020], [0043], [0223].) The *'859 Publication* further teaches that this conversion rate may be used to determine an effective dose of glyceryl tri-[4-phenylbutyrate] to administer. (Ex. 1007 at [0144]–[0156], [0221]–[0223]; Ex. 1002 ¶ 106.) A POSA would have further understood that after administering glyceryl tri-[4-phenylbutyrate], the patient's urinary PAGN excretion may be measured to determine whether the dose should be adjusted. (Ex. 1002 ¶ 97; Ex. 1007 at [0224].)

Accordingly, based on the teachings of *Blau*, *Simell*, the *'859 Publication*, and *Brusilow '84*, as well as the knowledge of a POSA, dependent claim 11 would have been obvious. (Ex. 1002 ¶ 98.)

7. Dependent Claims 14 and 15

Claims 14 and 15 respectively depend from claims 3 and 6, and further require that the 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 ¶ 99.)

X. CONCLUSION

For the reasons above, Petitioner respectfully requests institution of IPR for Claims 1-15 of the '559 patent on the grounds presented.

Respectfully submitted,

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Certificate of Service

I hereby certify on this 1st day of April 2016, 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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