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Paper No. 49
Filed: September 29, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.

and

LUPIN LTD. and LUPIN PHARMACEUTICALS, INC.,
Petitioners,
v.

HORIZON THERAPEUTICS, LLC,[1]
Patent Owner.

Case IPR2015-01127[2]
Patent 8,404,215 B1

Before TONI R. SCHEINER, DEBORAH KATZ, and GRACE KARAFFA OBERMANN, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318 and 37 C.F.R. § 42.73

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[1] Patent Owner filed an Updated Mandatory Notice indicating that the name had changed from Horizon Therapeutics, Inc. to Horizon Therapeutics, LLC (Paper 47).

[2] Case IPR2016-00284, instituted on a petition filed by Lupin Ltd. and Lupin Pharmaceuticals, Inc., has been joined with this proceeding.

We instituted a trial under 35 U.S.C. § 314 to review challenges brought by Par Pharmaceutical, Inc. ("Par") against claims 1–11 of U.S. Patent No. 8,404,215 B1 (Ex. 1001 ("the '215 patent")) in the Petition (Paper 2 ("Pet.")). *See* Paper 13 ("DI").

After institution, Lupin Ltd. and Lupin Pharmaceuticals, Inc. (collectively, "Lupin") filed a petition based on the same grounds as the Par petition and putting forth arguments and evidence that are substantially identical to those put forth by Par. *See* IPR2016-00284, Paper 1. We instituted trial on the same challenges of that petition that we instituted trial in the current *inter partes* review and joined the two proceedings into this review. *See* IPR2016-00284, Paper 11. We refer to Par and Lupin as "Petitioners" in this decision.

Horizon Therapeutics, Inc. ("Patent Owner") filed a Response under 37 C.F.R. § 42.120 (Paper 38[3] ("PO Resp.")) to Petitioners' challenges and Par filed a Reply (Paper 28 ("Pet. Reply") and Paper 41). Patent Owner does not seek to amend its challenged claims under 37 C.F.R. § 42.121. A hearing was held on July 26, 2016. (Paper 48.)

The parties also filed motions to exclude evidence. *See* Papers 33 and 35.

We conclude that the challenged claims are unpatentable.

[3] Paper 38 is a corrected Patent Owner Response, which was authorized to allow correction of citations to Exhibit 2012. *See* Paper 37. Because this corrected Response was filed after Petitioner's Reply was filed, Par was authorized to file a supplement to its Reply (Paper 41) in order to respond to Patent Owner's arguments based on the correct citations.

A. Related proceedings

Petitioner Par and Patent Owner identify *Hyperion Therapeutics Inc. v. Par Pharmaceutical, Inc.*, Case No. 14-cv-00384 (E.D. Tex.), filed April 23, 2014 in the U.S. District Court for the Eastern District of Texas by Patent Owner, as a related matter. Pet. 6; Patent Owner's Initial Mandatory Notices filed June 17, 2015 at 3. Par indicates that Patent Owner served the complaint on April 29, 2014, alleging that Par has infringed two of its patents, including the '215 patent.

Petitioner Lupin identifies a complaint filed by Patent Owner against Lupin in the United States District Court for the District of New Jersey (Case No. 1:15-cv-07624-RBK-JS) as a related matter. Lupin represents that Patent Owner asserted that Lupin infringes three United States patents, including the '215 patent in that complaint.

Patent Owner also represents that on April 1, 2016, Lupin filed a Petition for *inter partes* review of U.S. Patent 9,095,559, which issued from U.S. Patent Application 13/775,000 as a divisional of the '215 patent. *See* Patent Owner's Updated Mandatory Notices, Paper 10, identifying IPR2016-00829.

Par indicates that a second petition for an *inter partes* review of Hyperion's U.S. Patent 8,642,012 B1 was filed, but represents that the '215 patent is not related to that patent. Pet. 7.

Petitioners rely on the following prior art references in the challenges to Patent Owner's claims upon which this trial was instituted:

Abbreviation	Citation	Exhibit Number
Fernandes	INBORN METABOLIC DISEASES: DIAGNOSIS AND TREATMENT, 214–22 (J. Fernandes et al. eds., 3d ed. 2000).	1011
Blau	PHYSICIAN'S GUIDE TO THE LABORATORY DIAGNOSIS OF METABOLIC DISEASES, 261–76 (Blau et al. eds., 2d ed. 1996).	1006
Simell	Olli Simell et al., *Waste Nitrogen Excretion Via Amino Acid Acylation: Benzoate and Phenylacetate in Lysinuric Protein Intolerance*, 20 PEDIATRIC RESEARCH 1117–21 (1986).	1005
'859 Publication	U.S. Patent Publication No. 2010/0008859 A1, filed January 7, 2009, published January 14, 2010.	1008
Brusilow '91	Saul W. Brusilow, *Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion*, 29 PEDIATRIC RESEARCH 147–150 (1991).	1012
Brusilow '84	Saul W. Brusilow et al., *Treatment of Episodic Hyperammonemia in Children with Inborn Errors of Urea Synthesis*, 310 THE NEW ENGLAND JOURNAL OF MEDICINE 1630–34 (1984).	1004

The trial was instituted on challenges to the patentability of '215 patent claims 1–11 under 35 U.S.C. § 103 over the following groups of references:

Claim(s)	References
1, 3–7, and 9–11	Fernandes, Blau, Simell, and the '859 Publication
8	Fernandes, Blau, Simell, and Brusilow '91
2, 4–7, 9, and 10	Fernandes, Brusilow '84, Blau, and Simell

A.

Petitioners rely on the testimony of Neal Sondheimer, M.D., Ph.D. (Ex. 1002). Dr. Sondheimer testifies that he currently holds several positions at the Children's Hospital of Philadelphia and the University of Pennsylvania, including Attending Physician in the Division of Biochemical Genetics, Training Director for the Clinical Biochemical Genetics Group, Program Director for Medical Genetics, and Assistant Professor of Pediatrics. Ex. 1002 ¶ 10. Dr. Sondheimer testifies that he has been involved in several research studies about the treatment of urea cycle defects and has co-authored several publications about the use of ammonia-scavenging medications. *Id.* ¶ 12. We find Dr. Sondheimer to be qualified to provide opinions on the subject matter at issue.

Patent Owner does not present the testimony of its own witness to support its arguments.

B.

Under 35 U.S.C. § 103, subject matter is unpatentable "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007), the Supreme Court explained that, where there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, if the person of ordinary skill could have arrived at the claimed subject matter using common sense to combine different teachings of the prior art, then that subject matter is likely obvious, not innovative.

C.

We make the following findings of fact, which are supported by the preponderance of the evidence.

1. Nitrogen retention disorders are disorders that result from elevated levels of ammonia, a toxin, in a patient's blood. Ex. 1001, 1:14–16.

2. Nitrogen retention disorders include urea cycle disorders ("UCDs"), which are inherited deficiencies of the enzymes or transporters necessary to synthesize urea from ammonia. *Id.* 1:17–19.

3. UCDs and other nitrogen retention disorders can be treated with nitrogen scavenging drugs, which control a patient's ammonia levels. *Id.* 1:50–54.

4. Nitrogen scavenging drugs, such as PBA, NaPBA, and HPN-100, recited in claim 6 of the '215 patent, were known in the art before the priority date claimed for the '215 patent. *See* Ex. 1002 ¶ 21 (citing Ex. 1012, 147–48; Ex. 1015, 10–11, 13).

5. The '215 patent claims methods for the administration and dosing of nitrogen scavenging drugs to treat these disorders. Ex. 1001, 24:28–26:7.

6. Claim 1 of the '215 patent recites:

> A method for adjusting the dosage of a nitrogen scavenging drug in a subject who has previously been administered an initial dosage of the nitrogen scavenging drug, comprising:
>
> a) measuring a fasting blood ammonia level for the subject;
>
> b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level; and
>
> c) administering an adjusted dosage of the nitrogen scavenging drug, 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 blood ammonia level*.

Id. at 24:28–39 (emphasis added).

7. Claim 2 of the ’215 patent recites:

> A method of administering a nitrogen scavenging drug to a subject having a nitrogen retention disorder comprising:
> a) measuring a fasting blood ammonia level for the subject;
> b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level; and
> c) administering the nitrogen scavenging drug to the subject *if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level*.

Id. at 24:40–47 (emphasis added).

8. Claim 3 of the ’215 patent recites:

> A method of treating a subject with a nitrogen retention disorder who has previously been administered an initial dosage of a nitrogen scavenging drug comprising:
> a) measuring a fasting blood ammonia level for the subject;
> b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level; and
> c) administering an adjusted dosage of the nitrogen scavenging drug that is greater than the initial dosage *if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level*.

Id. at 24:48–57 (emphasis added).

9. Each of independent claims 1–3 of the ’215 patent recites administering a nitrogen scavenging drug “if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.” *Id.* at 24:28–57.

10. Fernandes teaches treating UCDs with nitrogen scavenging drugs, including sodium benzoate (which is recited in dependent claim 7) and phenylbutyrate. Ex. 1011, 219.

11. Fernandes states:

> All treatment must be monitored with regular quantitative estimation of plasma ammonia and amino acids, paying particular attention to the concentrations of glutamine and essential amino acids. The aim is to keep plasma ammonia levels below 80 µmol/l and plasma glutamine levels below 800 µmol/l.

Id. at 219.

12. Dr. Sondheimer testifies that Fernandes teaches that if the measured plasma[4] ammonia is greater than this 80 µmol/l upper limit, the dose of nitrogen scavenging drug should be increased. Ex. 1002 ¶ 39 (citing Ex. 1011, 219).

[4] We understand the terms "plasma" and "blood" are interchangeable for the purposes of this proceeding. *See* PO Resp. 4, n.2.

13. Figure 17.2 of Fernandes is reproduced below.

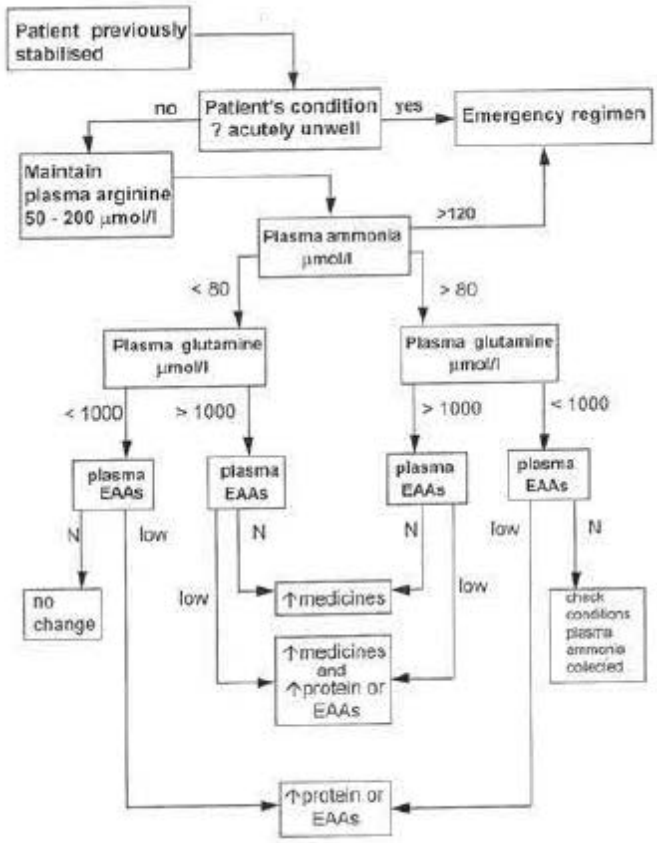

Figure 17.2 depicts a flow chart with guidelines for the management of patients with UCDs. Ex. 1011, 220.

14. The flow chart in Figure 17.2 of Fernandes provides one path for management of patients with UCDs wherein if the plasma ammonia level is either greater than or less than 80 µmol/l, then the levels of glutamine and essential amino acids in the plasma are evaluated. *Id.* at 220.

15. Dr. Sondheimer testifies that Figure 17.2 of Fernandes indicates that when a patient has a measured plasma ammonia value greater than the upper limit of normal, the initial dosage of nitrogen scavenging drug administered should be increased. Ex. 1002 ¶ 56.

16. Fernandes teaches increasing the dosage of sodium benzoate when patients experience acute emergencies. Ex. 1011, 219 ("Sodium benzoate is usually given in doses up to 250 mg/kg/day but, in acute emergencies, this can be increased to 500 mg/kg/day.").

17. Simell teaches measuring blood ammonia levels after an overnight fast in an experimental study of the effects of benzoate and phenylacetate. Ex. 1005, 1117–18.

18. Blau teaches measuring blood ammonia levels at least four hours after the last meal or intravenous amino acid supply when evaluating UCDs. Ex. 1006, 273.

19. The '859 Publication teaches adjusting the dose of a nitrogen scavenging drug according to a comparison of the subject's blood ammonia levels with the upper limit of normal for blood ammonia levels. Ex. 1008 ¶ 94 ("As used herein, 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. In certain clinical tests described herein the upper limit of normal for the subjects was between 26 and 35 µmol/L . . ."); *see also id.* ¶¶ 63, 201, Fig. 3.

20. Dr. Sondheimer testifies that those of ordinary skill in the art would have combined the teachings of Fernandes, Simell, Blau, and the '859 Publication because they relate to different aspects of using nitrogen scavenging drugs for treating UCDs. Ex. 1002 ¶¶ 44–47, 49.

21. Dr. Sondheimer testifies that in light of the teachings of Fernandes, Simell, Blau, and the '859 Publication those of ordinary skill in the art would have administered a dose of a nitrogen scavenging drug greater

than the initial dose if the measured fasting blood ammonia level was greater than the upper limit of normal. *Id.* ¶ 57.

22. Claim 8 of the '215 patent recites: "The method of claim 3 or 4, wherein administering an increased dosage of the nitrogen scavenging drug produces a normal average daily ammonia level in the subject." Ex. 1001, 25:3–5.

23. Brusilow '91 teaches treating with the nitrogen scavenging drugs phenylacetate or phenylbutyrate to bring daily plasma ammonia levels to 25.5 $\pm$ 3.3 µmol/L, wherein the upper limit of normal is less than 30 µmol/L. Ex. 1012, 149.

24. Dr. Sondheimer testifies that those of ordinary skill in the art would have been motivated to combine these teachings of Brusilow '91 with the teachings of Fernandes, Simell, and Blau, and that the combination teaches each and every element of claim 8. Ex. 1002 ¶¶ 65–67.

25. Brusilow '84 teaches treatments for increased blood ammonia levels in children with UCDs. Ex. 1004, 1631.

26. Brusilow '84 teaches that sodium benzoate and phenylacetate were administered to a patient who had a blood ammonia level measured at 11 µM (µmol/L). *Id.*

27. Dr. Sondheimer testifies that those of skill in the art would have understood the description of treatment of a patient with UCD in Brusilow '84 to be measuring blood ammonium level after a 24-hour fast. Ex. 1002 ¶ 79.

28. Dr. Sondheimer testifies that Brusilow '84 teaches comparing these fasting blood ammonia levels to the upper limit of normal for blood ammonia, and administering a dose of sodium benzoate and phenylacetate if

the measured blood ammonia level is greater than half the upper limit of normal. *Id.*

29. Dr. Sondheimer testifies that based on his review of the references, those of ordinary skill in the art would have combined the teachings of Brusilow '84 with the teachings of Fernandes, Simell, and Blau. *Id.* ¶ 96.

D.

In two separate challenges, Petitioners argue that independent claims 1–3 of the '215 patent are unpatentable over Fernandes, Blau, and Simell (claims 1–3), as well as either the '859 Publication (claims 1 and 3) or Brusilow '84 (claim 2). Pet. 12–23 and 30–38. Petitioners cite to Fernandes and the '859 publication for their teachings of measuring blood ammonia levels and increasing the dosage of nitrogen scavenging drugs when blood ammonia levels are greater than half the upper limit of normal. Pet. 13–14 (citing Ex. 1011, 219–220; Ex. 1008 ¶ 94; Ex. 1002 ¶¶ 39–61); *see* FFs 10–16. Petitioners cite to Simell and Blau for their teachings to measure blood ammonia levels after a fast. Pet. 13–14 (citing Ex. 1005, 1117–18; Ex. 1006, 273); *see* FFs 17–18. Petitioners also cite to Brusilow '84 for its teaching of measuring blood ammonia levels after a fast and administering drug if the measured level is greater than half the upper limit of normal. Pet. 30–31 (citing Ex. 1004, 1631; Ex. 1002 ¶ 79); *see* FFs 25–26. Petitioners' challenges are supported by the record, including the prior art cited and Dr. Sondheimer's testimony, which we credit.

Patent Owner argues that Petitioners have incorrectly interpreted the scope of the challenged claims and that, therefore, the cited prior art does not indicate the claimed methods are obvious. PO Resp. 4. According to Patent

Owner, its claimed methods are limited to an upper boundary by the recitation of administering drug "if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level." *Id*. at 4. Patent Owner characterizes its claimed methods as "targeting" blood ammonia levels that are greater than half the upper limit of normal. *See, e.g.*, *id*. at 32 (stating that "none of the cited references alone or in combination teaches or suggests that physicians should target a fasting blood ammonia of less than half the ULN for subjects having nitrogen retention disorders").

Patent Owner cites to references published before 2011 that allegedly highlight the problems of treating UCD patients, including the reported difficulties in controlling ammonia levels below the upper limits of normal and the reported uncertainty in relying on blood ammonia levels. *Id*. at 13–19. Patent Owner argues that its invention is targeting a blood ammonia level of half the upper limit of normal. *Id*. at 19–21. According to Patent Owner, half of the upper limit of normal is a lower target than previously considered, and this level should be measured in the fasting state. *Id*. Petitioners disagree with this interpretation.

Petitioners argue that the claims have no upper restriction in the determination of when to administer drug, as long as the blood ammonia level is above half the upper limit of normal, Pet. Reply 4–5, and do not require targeting of a fasting blood ammonia level, *id.* at 22–23. Thus, according to Petitioners, teachings to adjust the dose of nitrogen scavenging drug when the blood ammonia level is measured at any amount greater than half the upper limit of normal fall within the scope of the claims of the '215 patent.

We look to the language of the claim itself and to language in the specification to determine the scope of a claim. To limit a claim beyond what its plain language appears to convey, the patentee "may demonstrate an intent to deviate from the ordinary and accustomed meaning of a claim term by including in the specification expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1365 (Fed. Cir. 2004)

The plain language of independent claims 1–3 recites only the steps of "measuring," "comparing," and "administering." The claims do not include a "targeting" step or steps such as repeated measuring, comparing, and administering, until the fasting blood ammonia level is less than half the upper limit of normal. *See* Pet. Reply 5–6. Although Patent Owner cites to evidence of the background of the invention, we have not been directed to evidence within the specification of the '215 patent that clearly limits the claimed methods from being applied at any blood ammonia level greater than half the upper limit of normal. In addition, Patent Owner does not direct us to testimony or other evidence indicating that those skilled in the art would have considered the language of the claims to require "targeting" a certain blood ammonia level or to specify administering drug dosages only when the blood ammonia level is at about that targeted level. On the contrary, the plain terms of the claims contain no such limitations and are broad enough to embrace the administration of drug at higher blood ammonia levels.

Accordingly, we conclude that the correct interpretation of Patent Owner's claims is a method of measuring a fasting blood ammonia level, comparing this level to the upper limit of normal, and administering drug

when the level is *any* level greater than half the upper limit of normal for blood ammonia level.

E.

Patent Owner's arguments against the citation of specific prior art by Petitioners in their challenges to independent claims 1–3 rely on Patent Owner's claim interpretation, which we do not accept for the reasons stated above. For example, Patent Owner argues that Fernandes fails to teach or suggest that half the upper limit of normal is the safe upper limit for blood ammonia levels in patients. PO Resp. 32. Similarly, Patent Owner argues that Brusilow '84 does not teach targeting a fasting ammonia level of half the upper limit of normal. *Id*. at 44–45. Because claims 1–3 do not require targeting, achieving, or maintaining a safe level of blood ammonia, we are not persuaded by this argument.

Patent Owner argues further that Fernandes does not teach comparing blood ammonia levels to the upper limit of normal because it teaches relying on the measurement of 80 µmol/l, which is at least three times higher than the upper limit of normal according to Patent Owner. *Id*. at 33. Patent Owner cites to Dr. Sondheimer's cross-examination testimony to support its argument. In the portion cited, Dr. Sondheimer testifies about the upper limit of normal recited in a different reference (Ex. 1006, Table 11.5) in regard to patients four months old or older. *See* PO Resp. 34–35 (citing Ex. 2012, 156:19–157:3). In contrast, Dr. Sondheimer testifies elsewhere that in the context of Fernandes, the upper limit of normal is 80 µmol/l because Fernandes teaches that the aim is to keep plasma ammonia levels lower than 80 µmol/l. *See* Pet. Reply 12–13 (citing Ex. 2012, 151:15–152:1). We credit this latter testimony of Dr. Sondheimer because it is supported by

Fernandes,which teaches that the aim is to keep plasma ammonia levels lower than 80 µmol/l. (*See* FF 11.) Patent Owner does not direct us to evidence that one of skill in the art would have read Fernandes differently.

Patent Owner makes similar arguments against the teachings of the '859 publication, which was cited by Petitioner in the challenges to independent claims 1 and 3. Specifically, Patent Owner argues that the '859 publication teaches blood ammonia levels at 40 µmol/l, which are much higher than half the upper limit of normal according to Patent Owner. PO Resp. 42 (citing Ex. 1008 ¶ 94). Because a teaching to administer drug when the blood ammonia level is at *any* level above half the upper limit of normal meets the limitations of Patent Owner's claims 1–3, we are not persuaded by this argument.

F.

Patent Owner argues against Petitioner's challenges by asserting that the cited prior fails to teach relying on blood ammonia levels because they teach relying on plasma glutamine levels to determine drug dosages instead. PO Resp. 35. According to Patent Owner, Dr. Sondheimer omits the parts of Fernandes that teach measuring and using glutamine levels to determine drug dosing. *Id.* Patent Owner points to Figure 17.2, asserting that it teaches drugs should not be administered when plasma glutamine levels are less than 1000 µmol/l, even if plasma ammonia levels are greater than 80 µmol/l. *Id*. at 36 (citing Ex. 2012, 150:25–151:12). Patent Owner also cites to the text of Fernandes, which discusses the importance of glutamine levels. *Id*. at 36 (citing Ex. 1011, 219). According to Patent Owner, "Fernandes clearly teaches that a patient's plasma glutamine and *not* plasma ammonia

level dictates whether to increase the dosage of nitrogen scavenging medications." PO Resp. 35.

Patent Owner supports this argument further by citing to Blau, which reportedly cautions against overreliance on blood ammonia levels. PO Resp. 41 (citing Ex. 1006, 275 ("Overtreatment with excessively restricted essential amino acids . . . is a major problem with inexperienced teams, who focus primarily on the ammonia levels.")).

Despite Patent Owner's arguments, we are persuaded that the prior art teaches administering an adjusted dose of nitrogen scavenging drugs when blood ammonia levels are greater than half the upper limit of normal. While Fernandes may give instructions to increase drugs when other indicators are high, it also expressly teaches to increase drugs when plasma ammonia levels are greater than 80 µmol/l. On its face, Fernandes supports Dr. Sondheimer's testimony that Figure 17.2 teaches if the patient's measured plasma ammonia level is greater than 80 µM (µmol/l), the dosage of nitrogen scavenging drug should be increased. Ex. 1002, ¶ 48. Patent Owner does not direct us to evidence that one of skill in the art would have understood Fernandes differently. Without such evidence, we are not persuaded that because Fernandes and other references also teach considering glutamine levels when determining whether to increase drug dosages, the teachings regarding high ammonia levels would be ignored.

G.

Patent Owner argues that Fernandes and the '859 publication each teach away from reliance on blood ammonia levels when determining an effective dose of nitrogen scavenging drugs. PO Resp. 41–42. To support this argument, Patent Owner cites to the teaching in the '859 publication that

"adjusting of the initial dosage is done based on the amount of urinary PAGN, without relying upon plasma levels of PAA, PBA, or PAGN, and preferably without relying upon plasma levels of ammonia." Ex. 1008 ¶ 99. Similarly, Patent Owner argues that Blau teaches away from the claimed methods, citing the teaching in Blau that "[o]vertreatment with excessively restricted essential amino acids (especially plasma isoleucine <25 µmol/L) is a major problem with inexperienced teams, who focus primarily on the ammonia levels." Ex. 1006, 275; *see* PO Resp. 41. According to Patent Owner, these references caution practitioners about the dangers of over-reliance on blood ammonia levels in making treatment decisions and teach away from the claimed methods. PO Resp. 41–43.

Petitioners argue that the specific teachings highlighted by Patent Owner are not presented in context. For example, Petitioners note that the '859 publication provides a preferred embodiment when discussing the levels of other indicators, but also teaches the option of using of blood ammonia levels in the same method. *See* Pet. Reply 18 (citing Ex. 1008 ¶ 98). Petitioners argue that regardless of other methods and options known to those in the art, Dr. Sondheimer testifies that "[i]it was well known before the priority date of the '215 Patent that when treating UCD patients, plasma ammonia levels should be measured regularly and compared to the [upper limit of normal]." Ex. 1002 ¶ 23; *see* Pet. Reply 18. Because UCDs cause elevated levels of the toxin ammonia in the blood (*see* PO Resp. 9), Dr. Sondheimer's testimony is reasonable and, therefore, persuasive.

Patent Owner does not direct us to contradictory testimony or testimony to explain the significance of the isolated portions of the prior art identified as teaching away. Even in isolation, the identified portions appear

to provide options for the artisan, not strict instructions to ignore blood ammonia levels. Accordingly, we are not persuaded that these isolated sentences would necessarily discourage those of skill in the art from measuring or comparing blood ammonia levels when determining dosing of nitrogen scavenging drugs, as Patent Owner argues. *See In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.").

In regard to Petitioners' challenge of claims 2, 5–7, 9, and 10, Patent Owner argues that Brusilow '84 does not teach measuring fasting blood ammonia levels merely because some of the some of the subjects happened to have not eaten. PO Resp. 43-44. But Dr. Sondheimer testifies that those of ordinary skill in the art would have understood the reference to teach measurement after a fast. *See* Ex. 1002 ¶ 79. We find Dr. Sondheimer's testimony persuasive and supported by Brusilow '84, which states that blood ammonia levels were measured after a 24 hour-fast. FF 27. Patent Owner does not direct us to contradictory testimony of how one of skill in the art would have interpreted the teachings of Brusilow '84. Furthermore, even if we agreed with Patent Owner that Brusilow '84 does not teach comparing measured fasting blood ammonia levels (PO Resp. 43–44), Simell and Blau teach measuring blood levels in a fasting state (*see* FFs 17 and 18).

H.

Petitioners rely on the testimony of Dr. Sondheimer to argue that those of skill in the art would have combined the teachings of the cited prior art because each reference teaches methods drugs and treating patients with

UCDs. Pet. 15, 24-25, 27-28, 31-32; *see* FFs 20, 24, 29. Patent Owner argues that Petitioners' challenges to independent claims 1–3 fail because there would have been no reason to combine Fernandes with the other cited references. Specifically, Patent Owner argues that Simell reports an experiment, not a treatment regime as discussed in Fernandes. PO Resp. 37–38. Patent Owner argues further that it would have been contrary to the purposes of the experiment in Simell to let the volunteer subjects eat, thus the reasons for fasting were unrelated to the treatment regimens of Fernandes. *Id*. at 39–40. Similarly, Patent Owner argues that Blau concerns diagnosis, not treatment. *Id*. at 38–39 and 40–41.

Although Dr. Sondheimer acknowledged these differences on cross-examination (*see* Ex. 2012, 162:19–163:3 and 163:20–164:1), it is still his opinion that those of skill in the art would have combined the teachings because each refers to measuring blood ammonia levels and administering nitrogen scavenging drugs. *See* Ex. 1002 ¶¶ 45–47. Dr. Sondheimer does not retract his testimony on cross-examination and we do not consider that acknowledging the differences in the purposes of the references contradicts his original testimony. We note that there is an absence of testimony or other evidence that refutes Dr. Sondheimer's testimony or that supports Patent Owner's arguments about how those of skill in the art would have understood or used the teachings in Simell and Blau. We note that an analysis of obviousness "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

I.

In regard to the claims that depend on independent claims 1–3, Patent Owner argues that Petitioners' challenges to claim 4 fail for the same reasons discussed above in regard to claims 1–3. PO Resp. 46–48. Claim 4 recites: "The method of any of claims 1-3, wherein the nitrogen retention disorder is selected from the group consisting of a urea cycle disorder and hepatic encephalopathy." Ex. 1001, 24:58–60. As discussed above, we are not persuaded by these arguments.

Similarly, Patent Owner argues that Petitioners' challenge to claim 8 is insufficient. Claim 8 recites: "The method of claim 3 or 4, wherein administering an increased dosage of the nitrogen scavenging drug produces a normal average daily ammonia level in the subject." Ex. 1001, 25:3–5. Patent Owner argues that Brusilow '91 teaches treating patients with the nitrogen scavenging drugs phenylacetate or phenylbutyrate to bring daily plasma ammonia levels to within what is determined to be the upper limit of normal in the reference. Ex. 1012, 149. Patent Owner argues that Brusilow '91 fails to teach individual plasma ammonia measurements or to make any dosing recommendations based on mean plasma ammonium values or recommendations concerning target levels in UCD patients. None of Patent Owner's arguments relate to elements of claim 8. We note that the argument that Brusilow '91 does not teach fasting ammonia levels for the patient studied relates to an element of claim 4, but this element is taught by the other references cited in Petitioners' challenge. *See* Ex. 1005, 1117-18; Ex. 1006, 273; FFs 17 and 18. Accordingly, we are not persuaded by Patent Owner's argument that Petitioners' challenge to claim 8 is deficient.

Patent Owner does not address dependent claims 5–7, 9, 10 and 11.

Claims 5–7, 9, and 10 of the ’215 patent provide further limitations on the methods of claims 1–3, including: limiting the type of nitrogen scavenging drug (claims 5–7), adding a step of determining the upper limit of normal blood ammonia level for the subject (claim 9), and defining the upper limit of normal (claim 10). Ex. 1001, 24:58–26:2. We agree with Petitioners that a preponderance of the evidence shows each of these additional elements is taught in the cited references. *See* Pet. 22–23, 28–29, and 36–38 (citing Ex. 1011, 219–20; Ex. 1004, 1631; Ex. 1008 ¶ 94; Ex. 1011, 219–20; Ex. 1002 ¶¶ 59–60 and 73–74).

Claim 11 recites: “The method of claim **5**, further comprising: d) measuring urinary PAGN excretion; and e) determining an effective dosage of the PAA prodrug based on a mean conversion of PAA prodrug to urinary PAGN of 60-75%.” Ex. 1001, 26:3–7. Petitioners cite to Fernandes as teaching treatment of a patient with a PAA prodrug[5] (such as phenylbutyrate) (Ex. 1011, 219–20) and to the ’859 Publication for its teaching that PAA prodrugs have a conversion rate of 60–75% into urinary PAGN (*see* Ex. 1008 ¶¶ 20, 43, 223). *See* Pet. 29–30 (citing Ex. 1002 ¶ 77). We agree with Petitioners that these teachings, along with the teachings of Fernandes, Simell, and Blau, render obvious claim 11 of the ’215 patent.

J.

[5] Dr. Sondheimer testifies that phenylbutyrate is a prodrug of phenylacetic acid (“PAA”), meaning that phenylbutyrate is converted into PAA in the body. Dr. Sondheimer testifies further that PAA, in turn, is converted to phenylacetyl glutamine (“PAGN”), which removes two ammonia ions as it is excreted from the body. Ex. 1002 ¶ 21. Patent Owner does not contest Dr. Sondheimer’s testimony, which we find persuasive.

Both parties filed motions to exclude evidence of the other. Petitioners argue that Patent Owner's Exhibits 2022 and 2024 should be excluded because they are not prior art to the '215 patent. Paper 25, 1–2. Even considering Exhibits 2022 and 2024, we are still persuaded that a preponderance of the evidence shows claims of the '215 are unpatentable. Accordingly, Petitioners' motion is dismissed as moot.

Petitioners also argue that Patent Owner relies on attorney argument to rebut Petitioners' challenges, effectively providing impermissible expert evidence, which Petitioners seek to exclude. (Paper 25, 2–6.) We dismiss Petitioners' argument because attorney argument is not evidence. *See Meitzner v. Mindick*, 549 F.2d 775, 782 (CCPA 1977) ("Argument of counsel cannot take the place of evidence lacking in the record."). Therefore, Petitioners' argument is improperly presented in a motion to exclude evidence. Nevertheless, the issue of evidentiary support for Patent Owner's arguments is addressed above.

Patent Owner argues that evidence relied upon by Petitioners should be excluded. Paper 33. Specifically, Patent Owner seeks to exclude certain portions of Dr. Sondheimer's cross-examination testimony and Exhibits 1031–1033. Patent Owner acknowledges that "[i]n its Reply (Paper 28), Petitioner has not attempted to rely upon the portions of Dr. Sondheimer's deposition transcript or the documents Patent Owner seeks to exclude." Paper 33, 2–3. We dismiss Patent Owner's motion as being moot. Because Patent Owner cannot point to where Petitioners rely on the testimonial evidence, having apparently not relied on it, we have no basis on which to determine whether the evidence is inadmissible and no basis on which to

exclude it. Furthermore, because Exhibits 1031–1033 have not been made of record in this proceeding (*see* Paper 33, 1), they cannot be excluded.

ORDER

Petitioners have demonstrated, by a preponderance of the evidence, that claims 1, 3–7, and 9–11 of the '215 patent are unpatentable over Fernandes, Blau, Simell, and the '859 Publication under 35 U.S.C. § 103(a).

Petitioners have also demonstrated, by a preponderance of the evidence, that claims 2, 4–7, 9, and 10 of the '215 patent are unpatentable over Fernandes, Brusilow '84, Blau, and Simell under 35 U.S.C. § 103(a).

Finally, Petitioners have demonstrated, by a preponderance of the evidence, that claim 8 of the '215 patent is unpatentable over Fernandes, Blau, Simell, and Brusilow '91 under 35 U.S.C. § 103(a).

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–11 of the '215 patent have been shown to be unpatentable;

FURTHER ORDERED that Petitioners' and Patent Owner's motions to exclude are dismissed.

This is a final decision. Parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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