IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

HYPERION THERAPEUTICS, INC., Plaintiff, v. PAR PHARMACEUTICAL, INC., Defendant.	)	C.A. No. 2:14-cv-00384-JRG-RSP

PAR PHARMACEUTICAL, INC.'S INITIAL INVALIDITY CONTENTIONS AND NON-INFRINGEMENT CONTENTIONS FOR U.S. PATENT NOS. 8,404,215 AND 8,642,012

Pursuant to Local Patent Rules 3-3, 3-4, and 3-8 of the Local Rules for the United States Eastern District of Texas, defendant Par Pharmaceutical, Inc. ("Par") serves its Initial Invalidity Contentions and accompanying document production to plaintiff Hyperion Therapeutics, Inc. ("Hyperion") for U.S. Patent Nos. 8,404,215 ("the '215 patent") and 8,642,012 ("the '012 patent") (collectively the "patents-in-suit").

These contentions are based upon information obtained by Par as of the date of this document, and Par's discovery and investigation in connection with this action continues. Par reserves the right to supplement or amend these contentions based on information learned through discovery, any claim construction entered by the Court, plaintiffs' response to Par's contentions, and expert discovery. Par incorporates by reference each of the invalidity contentions articulated in its *Detailed Statement of the Factual and Legal Basis for Par*

1. Claim 1 of the ’215 Patent Is Obvious over the Prior Art

The alleged invention of claim 1 is invalid because it is obvious over the prior art. The prior art set forth in Appendix A, either alone or in combination with one another, render these claims obvious. The following combinations are examples of invalidating combinations.

a) The Combination of the ’859 Publication and Endo

The method of claim 1 of the is generally directed to increasing the dose of a nitrogen scavenging drug if the blood ammonia level is too high, where too high is a blood level greater than one half of the upper limit of normal.

> Claim 1. 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**.

(bold emphasis added). Although the alleged discovery by the inventors was that a nitrogen scavenging drug should be administered to patients even if the blood ammonia level is within otherwise normal upper limits, the claims are not restricted to only increasing the drug dosage when the blood ammonia levels are between one-half the upper limit of normal and the upper limit of normal. In other words, claim 1 presumably covers a method of increasing the dose when the fasting blood ammonia level is greater than one half the upper limit of normal, but also, increasing the dose when the fasting blood level is greater than the upper limit of normal, or even

increasing the dose when the blood level is at extremely high levels and well-beyond the upper limit of normal.

One of ordinary skill in the art would increase the dose of the nitrogen scavenging agent if the fasting blood ammonia level of a patient was at the upper limit of normal, simply to protect the patient from dangerously high levels. One of ordinary skill in the art was also motivated to increase the dose of the nitrogen scavenging agent if the fasting blood ammonia level was at, or above, one half of the upper limit of normal.[3]

U.S. Publication 2010/0008859 ("the '859 publication") teaches a method for determining when to increase a dosage of a nitrogen scavenging drug in a subject. ('859 publication at [0020], [0039].)[4] In particular, it teaches adjusting the schedule and dose of orally administered nitrogen scavenging drugs for patients already receiving the nitrogen scavenging drug. (*Id*. at [0044].) The prior art method comprises: a) measuring a fasting blood ammonia level (*id.* at [0212]) for the subject (*id.* at [0213]); b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level (*id.* at [0201]), plasma upper limit of normal (*id.* at [0094]), to determine whether to increase the dose of a nitrogen scavenging drug (*id.* at [0041]), wherein the dose needs to be increased if the fasting blood ammonia level is

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[3] It would have been obvious to a person of ordinary skill in the art to increase the drug dose even when the blood ammonia level was within normal limits, but above one half of the upper limit of normal because protein rich foods can impact circulating ammonia levels. It was known to lower circulating ammonia levels to ensure the value remains away from the upper limit of normal. Claim 1, however, is broader and covers even higher levels instances where the fasting blood ammonia levels are higher than even normal limits.

[4] The '859 publication is prior art to the '215 patent under 35 U.S.C. § 102(b) based on its January 14, 2010, publication date.

greater than half the upper limit of normal for blood ammonia level. If the ammonia control is inadequate, the dosage of the nitrogen scavenging drug can be increased. (*Id*. at [0083].)

Endo, F. et al., *Clinical Manifestations of Inborn Errors of the Urea Cycle and Related Metabolic Disorders during Childhood*, J. Nutrition 1606, 1606S, 1608S (2004) ("Endo 2004"), along with many other prior art references, teaches increasing the dose of a nitrogen scavenging drug when a person's blood ammonia levels are high, including greater than 100 µg/dL.[5] *See also, e.g.*, Batshaw, M. L., et al., *Alternative Pathway Therapy for Urea Cycle Disorders: Twenty Years Later*, 138 J. Pediatrics S46, S51 (2001) ("Batshaw 2001") ("The aim of long-term therapy is to maintain metabolic control with plasma ammonia concentrations less than twice normal"); The Urea Cycle Disorders Conference Group, *Consensus Statement from a Conference for the Management of Patients with Urea Cycle Disorders*, J. Pediatrics (Supplement) S1, S3 (2001) ("UCD Conference Group 2001") ("An elevated ammonia level during a clinic visit . . . does require adjustment of therapy or better compliance with recommended treatment regimen."); Lee 2010 at 226 (providing that increasing dose of a nitrogen scavenging drug may improve ammonia levels); Maestri, N.E., et al., *Long-Term Survival of Patients with Argininosuccinate Synthetase Deficiency*, 127 J. Pediatrics 929, 932 (1993) ("Maestri 1993") (providing, generally, that larger dosage of sodium phenylbutyrate reduced hyperammonemic episodes).

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[5] Endo discloses summary data showing the relationship between circulating blood ammonia levels and mental injuries. It states that feeding is not possible when a patient has high circulating blood ammonia levels at onset, and therefore, the data in Figure 3 represent fasted levels. *Id.* at 1609S. The data in Figure 3 show that only patients with blood ammonium levels of less than 200 µg/dL consistently had good-moderate outcomes.

The following chart compares claim 1 to the prior art.

Claim 1 of the '215 Patent	'859 publication and Endo
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:	The '859 publication teaches a method of adjusting the dose of a nitrogen scavenging drug in a subject who had previously been administered an initial dosage of the nitrogen scavenging drug. ('859 publication at *et sequence*, including [0016], [0020], [0044], [0091], [0108].)
a) measuring a fasting blood ammonia level for the subject;	The '859 publication discloses measuring blood ammonia levels and includes analysis from fed and fasting subjects.[6] (*See, e.g.*, *id*. at [0091], [0212].)
b) comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level; and	The '859 publication generally discloses comparing a blood ammonia level to the upper limit of normal for the blood ammonia level. (*See id*. at [0060], [0063], [0094], and [0201]; *see also* Figure 13 (reproduced below).)
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.	The '859 publication discloses the need to adjust the dosage of an ammonia scavenging drug based on patient to patient variability depending on the severity of liver disease or the inherited enzymatic defect. Dose adjustments are required to compensate for the individual patient characteristics. (*See id*. at [0041], [0083].) Endo teaches administering an adjusted dosage greater than the initial dosage if the fasting blood ammonia level is high, i.e., greater than half the upper limit of normal. (*See* Endo at 1606S, 1608S.)

[6] Other prior art references teach that fasting blood ammonia levels should be measured to adjust the dosage of a nitrogen scavenging drug. *See, e.g.*, Majeed, K. I., *Hyperammonemia*, eMedicine (last updated Dec. 18, 2001) (stating that plasma ammonium fasting levels should be measured for monitoring of condition

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