IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.,
Petitioner,

v.

HORIZON THERAPEUTICS, LLC,
Patent Owner.

Case IPR2017-01768
Patent 9,095,559

REPLY DECLARATION OF NEAL SONDHEIMER, M.D., Ph.D.

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I, Neal Sondheimer, do hereby declare as follows:

I. INTRODUCTION

A. Qualifications

1. My background and qualifications are described in Section II of my initial declaration submitted in the proceeding on July 13, 2017 ("Initial Declaration") (EX1002, ¶¶7-13). I incorporate those qualifications by reference here. I am being compensated as set forth in my Initial Declaration (EX1002, ¶2), and I continue to have no personal or financial interest in Par or in the outcome of this proceeding.

B. Scope of Work

2. For this declaration, I was asked to review and discuss the declaration of Dr. Gregory M. Enns ("the Enns Declaration"). (EX2006.) I have also reviewed the Horizon's Patent Owner Response (Paper 22) ("Horizon's POR"). Nothing in the Enns Declaration or Horizon's POR alters or changes my opinions set forth in my Initial Declaration.

3. This declaration is a statement of my additional opinions in this matter and the basis and reasons for those opinions. In forming the opinions expressed in this declaration, I have relied upon my education, experience, and knowledge of the subject matter discussed. In addition to my Initial Declaration and the materials identified therein, I have also reviewed, considered, or relied upon documents and other materials, which are cited in the table below:

Exhibit No.	***Description***
2012	U.S. Patent Publication No. 2012/0022157, filed August 27, 2009, published January 26, 2012
2013	Tuchman & Batshaw, *Management of Inherited Disorders of Ureagenesis*, 12 The Endocrinologist 99–109 (2002). ("Tuchman").
2015	Broomfield & Grunewald, *How to Use Serum Ammonia*, 97 Arch. Dis. Child Educ. Pract. Ed. 72-77 (2011)
2018	Kasumov et al., *New Secondary Metabolites of Phenylbutyrate in Humans and Rats*, 32 Drug Metabolism and Disposition 10-19 (2004)
2019	Häberle et al., *Suggested Guidelines for the Diagnosis and Management of Urea Cycle Disorders*, 7 Orphanet J. Rare Diseases 1-30 (2012)
2025	Colloquium, *Consensus Statement from a Conference for the Management of Patients with Urea Cycle Disorders*, 138 J. Pediatrics S1-S5 (2001)
2031	Cheson et al., *Novel Therapeutic Agents for the Treatment of Myelodysplastic Syndromes*, 27 Seminars in Oncology 560-77 (John W. Yarbro, et al. eds., 2000)
2032	Scaglia et al., *Effect of Alternative Pathway Therapy on Branched Chain Amino Acid Metabolism in Urea Cycle Disorder Patients*, 81 Molecular Genetics and Metabolism, Supplement 1 S79-S85 (2004)
2046	Transcript of the Deposition of Dr. Neal Sondheimer, taken April 19, 2018

II. GROUND 1 OF PAR'S PETITION RENDERS THE CHALLENGED CLAIMS OBVIOUS.

4. From my review of the Enns Declaration and Horizon's POR, I understand Horizon to only argue that the prior art does not teach (1) adjusting doses in patients who have plasma ammonia levels between one-half the ULN and the ULN; and (2) using "fasting" plasma ammonia levels in making decisions

about drug dosing, with respect to Horizon's challenge to Ground 1 of Par's Petition. I disagree.

A. A POSA Would Have Increased Drug Doses for Patients Having "Normal" Ammonia Levels.

5. Dr. Enns states "Fernandes only suggests that plasma ammonia levels at emergency levels (i.e., >120 µmol/L) warrant dosage increases." (EX2006, ¶66.) And he states that "Fernandes defines the normal range for plasma ammonia as <50 µmol/L," not the <80µmol/L presented in Ferdandes's Figure 17.2. (*Id.* at ¶64.) But as I stated in my Initial Declaration, Fernandes clearly advises increasing the dosage of medication in patients with plasma ammonia levels <80µmol/L. (EX1002, ¶59.) And while Fernandes discloses 50µmol/L as one ULN, Fernandes also expressly discloses that "[h]ealthy neonates have slightly higher values." (EX1015, 217-18.) To that end, Blau describes hyperammonemia as being "plasma ammonia >80 in newborns or >50 µmol/L after 28 days postnatally." (EX1006, 5.) A POSA would also understand that 80µmol/L in Figure 17.2, therefore, is a reasonable ULN for some UCD patients, for example, newborns.

6. Fernandes's Figure 17.2 is reproduced below with a red box highlighting the branch of the treatment protocol for patients having a "normal" plasma ammonia:

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