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 IPR2017-01767
Patent 9,254,278

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 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 previous 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. THE '859 PUBLICATION DISCLOSES ALL THE ELEMENTS OF CLAIMS 1-3.

4. Horizon claims that "a [person of ordinary skill in the art ("POSA")] would not understand Example 3 to disclose that patient 1006 received an amount of GPB sufficient to produce a fasting plasma ammonia level that is necessarily less than half the ULN." (Paper 22 at 60.) Horizon states this is because "a POSA

would not assume [the fasting plasma ammonia level] was necessarily the lowest," and therefore, lower than 8.30µmol/L. (*Id.* at 62.) I disagree.

5. Example 3 of the '859 Publication discloses that Subject 1006 had a maximum plasma concentration, i.e., C_{max}, for the plasma ammonia level of 13µmol/L. (EX1004, [0201].) The '859 Publication reports that the ULN for the study sites in Example 3 was 26-35µmol/L. (*Id.*) One-half ULN would be in the range of 13-17.5µmol/L. The maximum plasma ammonia level of Subject 1006, therefore, was the same as the lowest end of the one-half ULN range, i.e., 13µmol/L. As a result of Subject 1006's maximum plasma ammonia level being 13µmol/L, at every other time point, Subject 1006 had to have had a plasma ammonia level lower than one-half ULN.

6. Further, the time-normalized area under the curve ("TN-AUC") provides an AUC value that is normalized based on values obtained from measurements taken at various points in a 24-hour period. A POSA, therefore, would have easily understood that the only way Subject 1006's TN-AUC can be 8.30µmol/L with a C_{max} of 13µmol/L, is if there were plasma ammonia levels that were measured to be lower than 8.30µmol/L.

7. Given that the fasting plasma ammonia level would have been one of the lowest measurements in the day and Subject 1006 had a maximum plasma ammonia level at one-half the lowest end of the ULN range, i.e., 13µmol/L, the

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