UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WATSON LABORATORIES, INC.
Petitioner

v.

UNITED THERAPEUTICS CORP.
Patent Owner

Cases[1] IPR2017-01621; Patent 9,358,240
IPR 2017-01622; Patent 9,339,507

SECOND DECLARATION OF DR. WERNER SEEGER

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[1] The word-for-word identical paper is filed in each proceeding identified in the heading.

I, Dr. Werner Seeger, hereby declare as follows:

1. I am a named inventor of U.S. Patent No. 9,358,240 ("the '240 patent") and U.S. Patent No. 9,399,507 ("the '507 patent"), which are based upon U.S. provisional patent application No. 60/800,016 filed May 15, 2006 ("our patent application") (Ex. 2034). I am the director of University of Giessen and Marburg Lung Center ("UGMLC"), a research center at the University Hospital Giessen studying pulmonary hypertension.

2. I am a paid consultant for United Therapeutics Corporation in connection with IPR2017-01621 and IPR2017-01622. My compensation does not depend on the content of this declaration, the substance of any other testimony that I may offer in connection with this proceeding, or the disposition of this proceeding.

3. I am a co-author of the German language article: Hossein Ardeschi Ghofrani *et al*. "Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie,"[2] *Herz*, 30, 4 (June 2005): 296-302 ("the Ghofrani article") (Ex. 2103). I understand that Watson Laboratories, Inc. ("Watson") submitted an

[2] The title is translated as "New therapies in the treatment of pulmonary hypertension" in Exhibit 1005.

English language translation of the Ghofrani article in this proceeding as Exhibit 1005, which I have reviewed along with the original German article (Ex. 2103).

4. As stated in my previous declaration (Ex. 2020), the Ghofrani article was an overview review article, drafted under my direction and control by members of my research center at University Hospital Giessen. The intent of the article was to compile and review information regarding treatment of pulmonary hypertension, not to communicate primary data or to teach any specific therapeutic regimen.

5. As detailed in my previous declaration, Dr. Voswinckel and I contributed the following inhaled treprostinil section of the Ghofrani article:

> Initial trials in Giessen have shown proof of efficacy of inhaled treprostinil for the effective reduction of the pulmonary vascular resistance (PVR) [6]. In this first study, 17 patients with severe pre-capillary pulmonary hypertension were administered inhaled treprostinil (15 mcg/inhalation). This led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min. In direct comparison with inhaled iloprost, inhaled treprostinil showed a stronger pulmonary selectivity, so that it is possible to increase the dosage to up to 90 mcg (absolute inhaled dose per inhalation exercise) without adverse effects occurring [6]. Due to these unique properties (pronounced pulmonary selectivity and long duration of action after an individual inhalation), it is possible to reduce the number inhalations necessary to up to four per day; the inhalation period can be reduced to < 1 min. by selecting a suitable device. Additionally, the initial data shows that it is technically feasible for there to be only one to two breaths in an application.

(Ex. 1005, p. 3). Although the information in this excerpt for the article was compiled and composed by Dr. Voswinckel and myself, the individuals who

designed the underlying clinical studies with inhaled treprostinil are the same as the ones listed as inventors on the patents, as explained in more detail below. We of course performed the studies discussed in the Ghofrani article, wrote the excerpt quoted above, and submitted it for publication before it was published in June 2005 based upon our work together designing the clinical study.

6. Regarding dosage of inhaled treprostinil, the above excerpt from the Ghofrani review article notes that patients were "administered inhaled treprostinil (15 mcg/inhalation)." The word "inhalation" in that sentence (in both German and English) does not mean "breath," but rather, refers to an inhalation event. This is clear under our typical use of that terminology and because the above excerpt is citing the reference of endnote "[6]" for support, which used an inhalation period of six minutes (reference [6] of Ex. 1005 is Ex. 1046, and p. 5 of Ex. 1046 states that "6 min" was used). An inhalation event of six minutes indicates that a continuous nebulizer was being used (without pulsing or an opto-acoustical trigger), as in the first two studies using Optineb discussed below.

7. Although Ghofrani states that treprostinil showed a strong pulmonary selectivity "so that it is possible to increase the dosage to up to 90 mcg (absolute inhaled dose per inhalation exercise)," it does not report that this dosage was applied in human pulmonary hypertension patients, which is evident from reviewing the cited reference, "[6]" (Ex. 1046), in which this this dosage is not

reported. Rather, the Ghofrani review article states only that it "is possible" ("möglich ist" in Ex. 2103). This statement was intended to convey the idea that it may be possible to increase the dosage to that level, not that the referenced study actually performed that particular test. Similarly, the Ghofrani review article states that due to certain unique properties of treprostinil, "it is possible ["ist es möglich" in Ex. 2103] to reduce the number [of] inhalations necessary to up to four per day" and that the inhalation period "can be" reduced ["lässt sich bei" in Ex. 2103] to < 1 min. and that it "is technically feasible ["technisch realisierbar sein wird" in Ex. 2103] for there to [sic] only one to two breaths in an application." These statements of possibilities do not report any conclusion of studies performed, which is evident from reviewing the cited reference, in which 6 min inhalation time was reported "[6]" (Ex. 1046), but rather, suggest only future paths for clinical studies.

8. In sum, the Ghofrani review article does not explain or teach any particular therapeutic regimen or necessary parameters. It merely provides a high-level overview of early investigations into inhaled treprostinil and some speculation for additional research. Similarly, the two Voswinckel references provided by Watson as Ex. 1003 and 1046, both of which are abstracts and not primary study reports, report only select and incomplete information of different studies. Although the specific parameters used and particulars of the studies

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