UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, INC.
Petitioner

v.

UNITED THERAPEUTICS CORPORATION
Patent Owner

Patent No. 10,716,793 B2
Issue Date: July 21, 2020
Title: TREPROSTINIL ADMINISTRATION BY INHALATION

Inter Partes Review No. IPR2021-00406

DECLARATION OF DR. HOSSEIN A. GHOFRANI

4841-4517-6795

I, Dr. Hossein A. Ghofrani, hereby declare as follows:

1. I am a member of University of Giessen and Marburg Lung Center ("UGMLC"), a research center at the University Hospital Giessen studying pulmonary hypertension.

2. I am not a paid consultant for United Therapeutics Corporation, which I understand is the assignee of U.S. Patent No. 10,716,793.

Ghofrani Review Article

3. I am a co-author of the German language article: Hossein Ardeschir Ghofrani *et al*. "Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie,"[1] *Herz*, 30, 4 (June 2005): 296-302 ("the Ghofrani article"). I understand that Liquidia Technologies, Inc. ("Liquidia") submitted this publication along with an English language translation of the article in this proceeding as Exhibit 1010, which I have reviewed.

4. I have experience in the use of phosphodiesterase inhibitors for treatment of pulmonary hypertension. Therefore, I was asked by Dr. Werner Seeger to draft and, indeed, drafted the section of the Ghofrani article relating to phosphodiesterase inhibitors. In Exhibit 1010, this section in English begins at the

[1] The title is translated as "Pulmonary hypertension – new aspects of therapy" in Exhibit 1010.

bottom of page 11 and continues through page 13. Dr. Seeger and I also jointly drafted the sections on vasoactive therapy, inhaled iloprost, combination therapies, and treatment of early forms of treatment of pulmonary hypertension, as well as the introduction. In line with the normal practice in the UGMLC research center, I was included as the first author on the Ghofrani article for these significant contributions.

5. I did not make material contributions to any other section of the Ghofrani article, and I specifically did not contribute to the following excerpt:

> 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. 1010, p. 11). The information in this excerpt was compiled and composed by Dr. Robert Voswinckel and Dr. Werner Seeger, and the idea to perform the underlying work originated with at least them.

6. The section of the Ghofrani article relating to selective endothelin A receptor agonists was drafted by Dr. Friedrich Grimminger and Dr. Frank Reichenberger; both having experience in this field. In Exhibit 1010, this section is in English on page 11.

Voswinckel 2006 Clinical Observation Letter

7. I am listed as a co-author of the clinical observation letter: Robert Voswinckel, Hossein A. Ghofrani, Friedrich Grimminger, Werner Seeger, and Horst Olschewski "Clinical Observations" on "Inhaled Treprostinil for Treatment of Chronic Pulmonary Arterial Hypertension," "Letters" Section of the Annals of Internal Medicine, 144(2):149-50 (January 2006) ("Voswinckel 2006"). I understand that Liquidia submitted the letter in this proceeding as Exhibit 1009, which I have reviewed.

8. I am listed as a co-author on the Voswinckel 2006 clinical observation letter because it was and is the practice of our group to include as authors of abstracts and summary review articles the members of our group who contribute to or oversee any part in the trials, clinical routine management, or related parallel studies, not just members who were directly responsible for conceiving, analyzing,

and designing a particular study. This is typical of our group and a valid publication practice.

9. This same publication practice is reflected in other abstracts, such as: Voswinckel, R., *et al.*, Abstract 218: "Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension," *European Heart Journal* 25:22 (2004) ("Voswinckel JESC") and Robert Voswinckel, *et al.*, Abstract 1414: "Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension," Abstracts from the 2004 Scientific Sessions of the American Heart Association, *Circulation,* 110(17 Suppl.):III-295 (October 26, 2004) ("Voswinckel JAHA"), which I understand Liquidia submitted in this proceeding as Exhibit 1007 and Exhibit 1008, respectively.

10. In each of Voswinckel JESC and Voswinckel JAHA, I am listed as a co-author on that abstract because it was and is the practice of our group to include as authors of abstracts and summary review articles the members of our group who contribute to or oversee any part in the trials, clinical routine management, or related parallel studies, not just members who were directly responsible for conceiving, analyzing, and designing a particular study.

11. In the case of any studies of inhaled treprostinil described in these documents (Voswinckel 2006, Voswinckel JESC and Voswinckel JAHA), I was listed as a co-author because I assisted with the clinical responsibilities of

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