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APOTEX INC., APOTEX CORP., ARGENTUM PHARMACEUTICALS LLC, ACTAVIS ELIZABETH LLC, TEVA PHARMACEUTICALS USA, INC., SUN PHARMACEUTICAL INDUSTRIES, LTD., SUN PHARMACEUTICAL INDUSTRIES, INC., AND SUN PHARMA GLOBAL FZE,

Petitioners,

V.

NOVARTIS AG,

Patent Owner.

Case IPR2017-00854[1]

U.S. Patent No. 9,187,405

THIRD DECLARATION OF LAWRENCE STEINMAN, M.D.

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[1] Cases IPR2017-01550, IPR2017-01946, and IPR2017-01929 have been joined with this proceeding.

I, Lawrence Steinman, M.D., declare as follows:

I. Introduction

1. I am the same Lawrence Steinman who submitted a prior declaration in this matter, Exhibit 2022 ("First Declaration"). I also executed an additional declaration, Exhibit 2077 ("Second Declaration"), which was served on December 5, 2017 as supplemental evidence. I submit this Third Declaration in support of Novartis's sur-reply, and in particular to address certain opinions by Dr. Leslie Z. Benet (Ex. 1047). I use the same terms and abbreviations here that I used in my prior declarations.

2. In my First Declaration (Ex. 2022), I showed how the art taught away from the '405 Patent's invention—methods of using a 0.5 mg daily dosage of fingolimod to (a) prevent, reduce, or alleviate relapses in relapsing-remitting multiple sclerosis (RRMS) (claims 1 and 2); (b) treat the disease (claims 3 and 4); or (c) slow its progression (claims 5 and 6). (Ex. 1001 at 12:49-13:9.) Scientists in June 2006 believed that fingolimod worked primarily by sequestering lymphocytes out of the blood stream in the lymphatic system. That mechanism was thought to prevent the lymphocytes from attacking either transplanted organs or the body's own tissues in an autoimmune disease.

3. With respect to RRMS in particular, the Webb paper reported that experiments in an EAE animal model showed that "a threshold of about 70%

depletion of peripheral lymphocytes was required to see any efficacy[.]" (Ex. 2014 at 118.) That was consistent with data from transplant studies showing fingolimod effective only at about 80% suppression. But human transplant studies of fingolimod in Kahan 2003 (Ex. 1031) and Park 2005 (Ex. 1019) showed that 0.5 mg daily suppressed average lymphocyte by less than 50%. Scientists believed this transplant data applied to RRMS patients too, and thus pointed away from the 0.5 mg daily dosage claimed in the '405 Patent.

4. Dr. Benet does not appear to disagree with many of these facts, including that (i) lymphocyte suppression was viewed as the central mechanism of action for fingolimod in June 2006; (ii) prior studies showed that higher doses tended to suppress lymphocytes to a greater extent than lower doses, and produce better clinical outcomes; (iii) Webb provided a benchmark for potential human efficacy; and (iv) PK/PD data from transplant patients applied to RRMS patients too.

5. But Dr. Benet implies (Ex. 1047 at ¶¶ 20-22) that any prior art about the dose's likely efficacy is irrelevant here because the '405 Patent's claims allegedly require no efficacy. If the claims do require efficacy, Dr. Benet argues (Ex. 1047 at ¶¶ 46-48) that a person of skill would have viewed Webb's 70% suppression efficacy threshold as inconsistent with data in that paper pointing to a 60% threshold. Dr. Benet then says (*id.* at ¶¶ 49-62) that maximum rather than average suppression data in Kahan 2003 and Park 2005 meet Webb's alleged 60%

threshold, and (*id.* at ¶¶ 63-99) that other information in the art pointed toward 0.5 mg daily, including the instituted references (especially Kovarik).

6. Dr. Benet is an eminent pharmacologist, but his experience with MS, EAE models, and fingolimod is limited or non-existent. He testified on cross-examination that he has never published any peer-reviewed articles on any of these subjects (Ex. 2100 at 44:15-45:6); run an EAE experiment himself (*id.* at 45:25-46:2); or conducted any fingolimod experiments (*id.* at 44:2-17). His experience with MS drugs seems limited to a few confidential consulting projects 15-20 years ago, in which he "used" data from EAE studies. (*Id.* at 46:4-47:6.) Dr. Benet accordingly acknowledged that he is not an expert in MS research. (*Id.* at 41:18-42:15.)

7. This lack of experience pervades his declaration. In particular:

- Dr. Benet's contention that the '405 Patent's claims require no efficacy misunderstands the Patent and the state of MS drug research at the time of the invention.
- Dr. Benet's reading of Webb misunderstands EAE models, the data available to the authors, and the interpretation of that data by the authors.

- Dr. Benet's view that maximum rather than average lymphocyte suppression would guide dose development misunderstands the chronic nature of MS and the need for sustained treatment.
- Dr. Benet's interpretation of key references—especially Kovarik (Ex. 1004), Kataoka (Ex. 1029), and Kappos 2005 (Ex. 1007)—is colored by hindsight rather than knowledge of the field of MS drug research at the time.

8. I address each of these issues in further detail below. I also address a skilled person's view as of June 2006 of the meaning of the claimed phrases " dosing regimen" and "daily dosage" of fingolimod.

II. Analysis

A. Claim Construction

i. The '405 Patent Claims 0.5 mg Daily of Fingolimod for the Purpose of Achieving, or to Actually Achieve, Specific Effects

9. Dr. Benet argues (Ex. 1047 at ¶¶ 20-22) that the '405 Patent's claims require that 0.5 mg of fingolimod be given merely to a "subject in need" of the claimed effects. The claims supposedly do not require that the dose achieve those effects, or even be intended to do so. From this, Dr. Benet argues that the expected efficacy the 0.5 mg daily dosage would have been irrelevant to a person of skill evaluating whether the dose was obvious in June 2006.

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