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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

SECOND DECLARATION OF FRED D. LUBLIN, M.D.

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

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I, Fred Lublin, M.D., declare as follows:

I. Introduction and Summary

1. I previously submitted a declaration in this proceeding on May 2, 2017, Exhibit 2003. I respectfully incorporate that declaration by reference. I use the same abbreviations and terms here that I used there. I submit this new declaration to provide information about fingolimod's clinical trials.

2. I have been involved in clinical trials for almost every MS medication approved in the U.S. and Europe as of June 2006 and thereafter, as well as many that were never approved. I was involved in both the Phase II and Phase III human trials for fingolimod, as I describe further below.

3. The Phase III trial for fingolimod tested two doses, 1.25 mg and 0.5 mg daily. Counsel for Novartis has asked me whether the 0.5 mg dose was expected to be effective. The answer is no. I and others believed the likelihood was that 0.5 mg daily would be equivalent to placebo, *i.e.*, that it would show no efficacy. Even if it showed some efficacy, I am aware of no one who believed that dose would have the same efficacy as 1.25 mg daily. I was very surprised when 0.5 mg daily produced essentially the same results as that higher dose.

4. As I describe below, fingolimod's earlier Phase II MS trial had also tested two doses, 5.0 mg and 1.25 mg daily. Pre-clinical and clinical studies had suggested that fingolimod's efficacy was dose-dependent. I and others therefore

expected the 5.0 mg dose to be more effective than the 1.25 mg dose. We were surprised when the two Phase II doses showed essentially the same efficacy. Because the lower 1.25 mg daily dose had also shown slightly better safety, Novartis proposed to the U.S. FDA to confirm that dose's efficacy in Phase III studies.

5. FDA agreed to a Phase III trial for 1.25 mg daily but asked Novartis to evaluate a lower dose too. At the time, a recent incident involving another drug called "Tysabri" had prompted FDA to express extra concern about the safety of MS medications. FDA accordingly pressed to understand fingolimod's minimum effective dose. That would allow FDA and others to understand fingolimod's optimal balance between efficacy and safety.

6. Novartis included a 0.5 mg dose arm in the Phase III trials, but adopted a novel MS trial design to account for the scenario that a 0.5 mg daily dose would not be effective. A panel was tasked to conduct an early analysis of patients given 0.5 mg daily to evaluate if the dose was "futile" and should be discontinued before the full trial was finished. I have never been involved in a Phase III MS clinical trial that contained such an early "futility analysis" of one dose and not others.

7. Notwithstanding that feature of the Phase III trials, physicians remained concerned that 0.5 mg daily would be ineffective. A review panel at my own hospital Mount Sinai in New York City balked at participating in one of the trials for fear that the 0.5 mg dose would be no more effective than placebo.

8. It thus came as a total surprise when 0.5 mg daily proved to be not only effective, but essentially just as effective as 1.25 mg daily. That unexpected result meant that FDA still did not have enough information to know fingolimod's minimally-effective dose. FDA accordingly approved fingolimod on condition that Novartis conduct a post-marketing "Phase IV" study of an even lower dose, which ended up to be 0.25 mg daily. That study's results are not yet available. In addition, others in the field conducted further experiments in search of fingolimod's dose-response curve in smaller studies that I describe below. If fingolimod's efficacy at 0.5 mg daily would have been obvious in June 2006, then FDA and Novartis would have started testing these lower doses at the outset, rather than wait until after the Phase III trial.

9. I describe these facts in more detail in the paragraphs to follow. I first summarize my experience with MS clinical trials generally. I then describe the fingolimod clinical trials, including a background on MS clinical trials and a description of the fingolimod Phase I-III trials as well as post-marketing research.

10. I was first retained to provide expert advice on Gilenya®-related litigation in April 2015. In preparing my testimony in this declaration, I have worked approximately 62 hours, including many hours conducting my own research into the prior art. I have spoken with counsel and reviewed and commented upon drafts they prepared based on our discussions. I have thoroughly reviewed the contents of my

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