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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

DECLARATION OF JEROLD CHUN, M.D., PH.D.

Mail Stop Patent Board
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
ALEXANDRIA, VA 22313-1450

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

I, Jerold Chun, M.D., Ph.D., declare as follows:

I. Introduction

1. I am a non-practicing M.D. and neuroscientist currently running a lab at the Sanford Burnham Prebys Medical Discovery Institute. Among other things, I research drugs like fingolimod that affect the sphingosine 1-phosphate (SIP) signaling system in the body. I was a co-author of the Webb reference (Ex. 2014) and headed the department and analyzed data from scientists who conducted the experiments Webb reports. Novartis has asked me to address the declaration of pharmacologist Dr. Leslie Z. Benet in this matter (Ex. 1047), focusing in particular on Dr. Benet's interpretation of the Webb reference.

2. In Webb, my research team and I reported on experiments we conducted with fingolimod while at Merck Research Laboratories. We tested fingolimod (also called FTY720, or just FTY) in an accepted multiple sclerosis (MS) animal model, the experimental autoimmune encephalitis (EAE) system. (Ex. 2014 at 108.) Our version of EAE used mice and had several unique features that I discuss below.

3. Before we did our experiments, multiple papers had reported that fingolimod was a novel immuno-modulator. Scientists believed fingolimod worked primarily by interacting with the sphingosine pathway in the body to induce lymphocytes to die or to remain in lymph nodes and out of circulating blood.

Unpublished data at the time supported the involvement of S1P receptors, which could be involved in the disruption of lymphocyte trafficking and egress from lymph nodes. This in turn could reduce the number of pathogenic, circulating lymphocytes available to participate in an adverse immune system reaction, such as by attacking a newly-transplanted organ or the body's own tissues as part of an autoimmune disease.

4. This mechanism for modulating the immune system was unlike any others that had been discovered before. Prior immuno-modulators had acted primarily either by killing immune system cells or inhibiting their multiplication in the body in response to a stimulus. Emerging data suggested that fingolimod instead was involved in redirecting trafficking of immune system cells within the body. (*Id.*) Given ambiguity and uncertainties about this new apparent mechanism of action, much was unknown about fingolimod's potential use in humans for treating MS.

5. When we conducted the experiments reported in Webb from 2000-2002, reducing the number of lymphocytes circulating in the blood had already been reported as a likely marker of efficacy in organ transplant experiments.[2] One of our

[2] Dr. Benet and others in this proceeding call this mechanism "lymphocyte suppression." At the time, we called this mechanism "lymphopenia," or

goals was to assess whether the same measure would be useful for MS. We concluded that lymphocyte suppression was an effective albeit incomplete marker of likely efficacy for the disease, and that "a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy" in the SJL mouse EAE model system. (Ex. 2014 at 118.).

6. Dr. Benet does not appear to question our general conclusion that lymphocyte suppression could be a useful efficacy marker so long as suppression surpassed a minimum threshold. Dr. Benet instead questions what that threshold was. He argues that Webb data shows that only 60% suppression was required for efficacy, not 70%. He bases that conclusion on the paper's description of the average effects of one dose in one group of tested mice. (Ex. 1047 at ¶¶ 40-48).

7. Dr. Benet appears to have misunderstood our paper. Our conclusion that 70% suppression was needed for "any efficacy" was the product of our collective judgment based on a totality of data presented in our paper. The average effect of one dose in one group of mice was just one piece of data. We also assessed the effects of different doses in individual mice; the ability of a dose to produce

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"lymphocyte sequestration." I will use the terminology Dr. Benet adopted in his declaration. My understanding is that the terms "lymphocyte suppression," "lymphopenia," and "lymphocyte sequestration" are synonymous here.

sustained clinical improvement; and other facts to reach our conclusions. As those with experience running EAE experiments know, the model has a subjective aspect that requires judgment-calls when interpreting results. Among other reasons, this is due to the inherently imprecise scoring system used to evaluate a clinical level of disease in tested rodents, as I discuss further below.

8. The nine researchers on our team concluded that about 70% suppression was needed for any efficacy in EAE, and the peer reviewers at the Journal of Neuroimmunology did not question that conclusion. Our goal had been to find a lymphocyte level that assured a clear and reproducible efficacy signal with FTY720 treatment. In this model, 70% and 60% are close and generally consistent with "about 70%" stated in our Discussion. In other words, our conclusion that about 70% reduction in peripheral blood lymphocyte levels was required for any efficacy was not a mistake; it was the result of collective judgment based on multiple data sources and an appreciation of the subjective nature of determining clinical scores in this model. Dr. Benet's critique of that judgment misunderstands the EAE system, and our paper.

9. I elaborate upon these issues further below, after first setting out my background and research experience.

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