UNITED STATE	S PATENT AND TRADEMARK OFFICE
BEFORE THE P	PATENT TRIAL AND APPEAL BOARD
ACTAVIS ELIZABETH LI PHARMACEUTICAL II	CORP., ARGENTUM PHARMACEUTICALS LLC, LC, TEVA PHARMACEUTICALS USA, INC., SUN NDUSTRIES, LTD., SUN PHARMACEUTICAL NC., AND SUN PHARMA GLOBAL FZE,
	Petitioners,
	V.
	NOVARTIS AG,
	Patent Owner.
_	Case IPR2017-00854 <sup>1</sup>
1	U.S. Patent No. 9,187,405

### DECLARATION OF LAWRENCE STEINMAN, M.D.

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

<sup>&</sup>lt;sup>1</sup> Cases IPR2017-01550, IPR2017-01946, and IPR2017-01929 have been joined with this proceeding.



Anotex v. Novartis

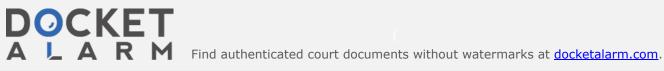
## TABLE OF CONTENTS

I.		Introduction and Summary	1
II.		Experience and Qualifications	5
III.		The June 2006 State of the Art and the Invention	9
	A.	Multiple Sclerosis	9
В.		Existing MS Therapies in June 2006	14
	C.	Fingolimod	16
	D.	Research into Fingolimod Dosing as of June 2006	21
		i. Transplant Studies	22
		ii. Fingolimod EAE Studies	33
		iii. Kappos 2005—Phase II Human MS Study	44
	E.	The Invention and Patent	46
	F.	Later Data Confirming the Invention's Surprising Results	53
IV.		Analysis of the Petition	55
	A.	The Person of Skill and Claim Construction	56
	B.	The Obviousness Grounds	60
		i. Teaching Away and Unexpected Results	60



# IPR2017-00854 nt No. 9,187,405

		ii. Ground 1: Kovarik and Thomson	U.S. Patent No. 9,187,405
		iii. Ground 2: Chiba, Budde, Kappos 2005	82
	C.	The Anticipation Ground: Kappos 2010	84
V.		Conclusion	87



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

#### I. Introduction and Summary

- 1. I am a physician with thousands of current and former multiple sclerosis patients; a researcher with over 550 publications related to neurological and immunological disorders; a professor at Stanford University; and a member of the National Academy of Sciences. I set out my full experience and qualifications below. I submit this declaration for Patent Owner Novartis AG in opposition to Petitioners' challenge to U.S. Patent No. 9,187,405.
- 2. The '405 Patent claims a method of dosing the drug fingolimod for patients with Relapsing-Remitting Multiple Sclerosis (RRMS). Novartis scientists Peter Hiestand and Christian Schnell discovered that doses less than half those previously thought effective could help victims suffering from the disease. Novartis applied for a patent in June 2006, and the U.S. Patent and Trademark Office (PTO) awarded claims to a 0.5 mg daily dose. Novartis sells fingolimod at that dose for RRMS under the brand-name Gilenya®.
- 3. Petitioners challenge the PTO's award of the Patent. Petitioners say references published before June 2006 would have made a 0.5 mg daily dose obvious to someone with skill in the field. In addition, the Patent's specification allegedly does not support parts of the claims, which Petitioners say opens the Patent to challenge as anticipated by a paper published after June 2006. In support of their



challenges, Petitioners rely on a declaration from an MS clinician, Dr. Barbara Giesser. (Ex. 1002.) The Petitions' challenges are misguided.

- 4. By June 2006, research had shown that fingolimod could suppress the immune system by sequestering white blood cell lymphocytes in lymphatic tissue away from the blood stream. Scientists believed this mechanism might protect against organ rejection and/or autoimmune diseases by reducing the number of circulating lymphocytes available to attack transplanted organs or the body's own tissues. One such autoimmune disease was RRMS, in which the body's immune system attacks the central nervous system (CNS).
- 5. Studies showed, however, that only substantial lymphocyte suppression provided any clinical benefit. Multiple papers reported that at least 80% reduction was needed to reduce organ rejection. Another paper—"Webb"(Ex. 2014)—found in an established RRMS model that "a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy[.]" (*Id.* at 118.) Less suppression correlated with no clinical benefit. Human studies further showed that only daily doses of 1.0 mg or higher could suppress lymphocytes to these levels. Lower doses could not, including 0.5 mg daily. Hence, the literature in June 2006 taught that 0.5 mg daily would not be effective for RRMS.
- 6. Hiestand and Schnell adopted a fresh perspective to discover otherwise. They used inventive techniques with an accepted MS model to focus later in the



# DOCKET

# Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

# **Real-Time Litigation Alerts**



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## **Advanced Docket Research**



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

### **Analytics At Your Fingertips**



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

#### API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

#### **LAW FIRMS**

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

#### **FINANCIAL INSTITUTIONS**

Litigation and bankruptcy checks for companies and debtors.

#### **E-DISCOVERY AND LEGAL VENDORS**

Sync your system to PACER to automate legal marketing.

