UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, INC., Petitioner,

v.

MERCK SERONO S.A. Patent Owner.

Case IPR2023-00481 U.S. Patent No. 8,377,903

DECLARATION OF AARON E. MILLER, M.D.

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VI.	State of the Art Prior to December 22, 200414							
	A.	Multiple sclerosis is a chronic disease with no known cure1						
	B.	Immunosuppression was a common therapeutic strategy to treat multiple sclerosis before December 2004						
	C.	Cladribine, a known immunosuppressant, was used to treat multiple sclerosis before December 2004						
		1.	Clinical studies assessing parenteral cladribine in MS patients began in the early 1990s	27				
		2.	By December 2004, oral cladribine was favored to treat MS patients	37				
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	C.	"Induction Period"						
	D.	"Maintenance Period"						
IX.	Basis	Basis of my analysis with respect to obviousness						
X.	My analysis with respect to claim 1750							



Inter Partes Review of U.S. Patent No. 8,377,903 Declaration of Aaron E. Miller, M.D. (EX1002)

A.		Bodor and Stelmasiak teach orally administering cladribine to reat multiple sclerosis, including RRMS				
B.	an "i	Bodor's and Stelmasiak's cladribine dosing regimens include an "induction period;" Bodor's induction period is 2 months long				
C.		odor teaches the claimed total dose of cladribine administered an induction period				
D.		Bodor and Stelmasiak teach retreating with cladribine after a cladribine-free period				
E.	Stelmasiak teaches administering a lower dose of cladribine in the retreatment period compared to the induction period; a POSA would have known how to optimize the maintenance period dose and length					
F.	Stelmasiak teaches a second cladribine-free period after the maintenance period; a POSA would have known how to optimize the length of the second cladribine-free period					
G.	A POSA would have been motivated to combine Bodor and Stelmasiak with a reasonable expectation of success					
	1.	A POSA would have been motivated to formulate an oral cladribine composition per Bodor	67			
	2.	A POSA would have been motivated to treat relapsing- remitting MS by administering Bodor's oral cladribine composition according to Stelmasiak's induction period/cladribine-free period/maintenance period/cladribine-free period framework	68			
	3.	A POSA would have been motivated to administer "about 1.7 mg/kg to about 3.5 mg/kg" in an induction period	74			
	4.	A POSA would have administered a lower total dose of cladribine in the maintenance period compared to the total dose in the induction period	75			



Inter Partes Review of U.S. Patent No. 8,377,903 Declaration of Aaron E. Miller, M.D. (EX1002)

	5.	ä	A POSA would have routinely optimized the prior art to arrive at the claimed total cladribine dose and length of the maintenance period	77
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I, Aaron E. Miller, M.D., hereby declare as follows.

I. Introduction

- 1. I am over the age of eighteen (18) and otherwise competent to make this declaration.
- 2. I have been retained as an expert witness on behalf of Petitioner Hopewell Pharma Ventures, Inc. ("Hopewell") for the above-captioned *inter partes* review ("IPR"). I am being compensated for my time in connection with this IPR at my standard consulting rate, which is \$790/hr.
- 3. I understand that the petition for IPR involves U.S. Patent No. 8,377,903 ("the '903 patent"), EX1001, which resulted from U.S. Application No. 12/766,173 ("the '173 application"), filed on April 23, 2010, which is a continuation of U.S. Application No. 11,722,018, which is the National Phase Entry of International Patent Application No. PCT/EP2005/056954, filed on December 20, 2005, which claims the benefit of the U.S. Provisional Application No. 60/638,669, filed on December 22, 2004, and the Foreign Patent Application No. EP04106909, filed on December 22, 2004. EX1001, De Luca. The '903 patent issued on February 19, 2013, from the '173 application. *Id.* The '903 patent names Giampiero De Luca, Arnaud Ythier, Alain Munafo, and Maria Lopez-Bresnahan as



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