

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, LLC,
Petitioner

v.

MERCK SERONO S.A.,
Patent Owner

Case IPR2023-00480
U.S. Patent No. 7,713,947

DECLARATION OF RODOLFO PINAL, PH.D.

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Hopewell EX1080
Hopewell v. Merck
IPR2023-00480

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I, Rodolfo Pinal, 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”) and related proceeding IPR2023-00481. I am being compensated for my time in connection with this IPR at my standard consulting rate, which is \$520/hr.

3. I understand that these IPR proceedings involve two patents, US Patent Nos. 7,713,947 (IPR2023-00480) and 8,377,903 (IPR2023-00481).

II. MY BACKGROUND AND QUALIFICATIONS

4. My Curriculum Vitae is submitted herewith as Exhibit 1081.

5. I am an Associate Professor of Industrial and Molecular Pharmaceutics (formerly Industrial and Physical Pharmacy) at Purdue University and the Director of Purdue's Dane O. Kildsig Center for Pharmaceutical Processing Research. Throughout my career, prominent areas of my research have included developing strategies for enhancing the bioavailability of poorly soluble drugs. I have over 25 years of experience in the area of pharmaceutical solids, including pharmaceutical salts, crystal polymorphs, amorphous systems, solid dispersions, pharmaceutical films, and tablets.

6. I received my undergraduate degree in biopharmaceutical chemistry from the National University of Mexico, followed by a year-long internship at the National General Hospital in Mexico City. I received my Ph.D. in Pharmaceutical Sciences with a minor in Physical Chemistry from the University of Arizona in 1988. My dissertation was titled “Estimation of Aqueous Solubility of Organic Compounds.” After completing my Ph.D., I completed post-doctoral training in Environmental Sciences at the University of Florida. My post-doctoral research focused on solution chemistry of complex mixtures.

7. In 2003, I joined the faculty at Purdue University, where I continue my employment to this day. My research at Purdue involves the study of some of the most prevalent issues encountered during pharmaceutical drug development, including drug solubilization and delivery. My research specifically includes solubility and related phenomena, from the standpoint of both the solid properties of the materials, and solution chemistry phenomena. My work focuses on solubilization and drug delivery of liquid mixtures; solid formulations, including crystalline and amorphous systems, as well as methods for enhancing oral bioavailability of poorly soluble active compounds; study of polymeric excipients and their interactions in pharmaceutical systems; pharmaceutical processing; and prefabricated dosage (tunable) forms. I also teach several undergraduate and graduate-level courses related to pharmaceutical technology and formulation, such

as Pharmaceutical Science Orientation, Parenteral Products (injectable), Dosage Forms I and II, and Biotechnology and Advanced Parenterals. In Dosage Forms I, I teach the foundation of the basic concepts of pharmaceutics that are the foundation of drug delivery, including the molecular basis for aqueous and liquid solubility of drugs, pharmacokinetic principles that are related to dosage forms, mechanisms by which excipients or manufacturing processes affect bioavailability, and how chemical kinetics apply to the shelf-life of dosage forms. In Dosage Forms II, I teach the factors involved in the use of generic versions of solid and liquid dosage forms and their influence on therapeutic outcomes.

8. I have also been a visiting Professor at the Shenyang Pharmaceutical University in Shenyang, China, teaching undergraduate and graduate students formulation aspects of solubility and solubilization of drugs and the physical characterization of pharmaceutical solids for industrial scientists, and serving as co-adviser of Master's and Ph.D. students in the department of Pharmaceutics. I have served on the Summer Faculty on Pharmaceutical Technology at Universidad de Los Andes in Bogota, Colombia.

9. Prior to joining the faculty at Purdue University, I worked at Hoffmann-La Roche Inc. for 13 years, from 1990 through 2003. While at Roche, I worked on the specialties of pre-formulation and formulation of sterile products and solid state pharmaceutics. My work at Hoffman-La Roche Inc. also involved

the physical and chemical characterization of new chemical entities as potential drug candidates. My responsibilities included experimental measurements of the solubility, hydrophobicity, and chemical stability of drug candidates. My work also included compatibility studies of drugs with different excipients. At Hoffman-La Roche Inc. I also developed injectable preparations for drugs in the development pipeline. I was assigned difficult to solubilize drugs, where I made extensive use of solubilization techniques, including *in situ* salt formation, complexation, and injectable emulsions.

10. I was also the leader of the Solid State Pharmaceutics group at Hoffman La-Roche from 1999–2003. My group was responsible for the physical characterization of all drug substances, excipients, and intermediate blends used in the New Jersey facility, predominantly for making tablets, but also including suspensions, emulsions and solution dosage forms. In this capacity, my responsibilities included the selection of the solid forms of drugs, such as crystal polymorphs, as well as amorphous systems and salt forms.

11. I have published dozens of papers and two book chapters on solubility and other solid state chemistry topics. I am also a peer reviewer on over three dozen journals, including *Journal of Pharmaceutical Sciences*, *Pharmaceutical Research*, *Crystal Growth and Design*, and *Drug Development and Industrial*

Pharmacy. And I have served as a proposal reviewer for the National Science Foundation since 2006.

12. I am a member of the American Chemical Society, the American Association of Pharmaceutical Scientists, and the Rho Chi Honor Society. My work in industry routinely involved participation in multi-disciplinary, drug development teams. Such teams included pharmacologists, toxicologists, pharmacokineticists, clinicians, formulation scientists, medicinal and analytical chemists and regulatory scientists.

13. In view of my education, experience, and expertise described above, I am an expert in the fields of pharmaceutical sciences, including drug formulation and development, pharmacology, and approaches for increasing oral bioavailability. Accordingly, I am an expert in the field of pharmacology.

III. SUMMARY OF OPINIONS

14. In this declaration, I consider cladribine dosage forms as disclosed by Bodor, Nicolas S. and Dandiker, Yogesh, “Oral Formulations of Cladribine,” International Patent Application Publication No. WO2004/087101 A2 (filed March 26, 2004, published October 14, 2004) (“Bodor,” EX1022) and Stelmasiak, Zbigniew, *et al.*, “A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis,” *Med. Sci. Monit.*, 1998, 4(1):4–8 (“Stelmasiak,”

EX1013), and other exhibits cited herein. A summary of my opinions follows. The references I cite in this Declaration reflect the general knowledge in the art.

15. Before December 22, 2004, it was well known in the art that solid oral drug delivery is generally preferable over liquid oral formulations. EX1065, 287. As Dr. Bodor conceded, there were “many reasons” for such preference, including “convenience, or cost, or compliance, stability.” EX1059, 61:18-62:2; EX1065, 287. Similarly, Dr. Meibohm conceded that because “an oral administration of a tablet is done by the patient themselves,” it is “easier to use than other[forms],” and therefore contributes to “convenience or patient adherence.” EX1062, 51:12–52:9. And among solid oral dosage forms, tablets were “the manufacturer’s dosage form of choice” because of their decreased cost of manufacture, increased stability, and tamper-resistance. EX1065, 287.

16. Considering the general preference in the art for oral tablets, a pharmacologist prior to December 22, 2004 would have advised a POSA (a person of ordinary skill in the art, as I discuss in ¶¶22) who desired to use cladribine to treat MS that Bodor’s oral cladribine tablets would be desirable for use in an oral cladribine regimen. Bodor teaches “compositions of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine” and are characterized as having “improved cladribine absorption, as reflected by higher bioavailability” and “lower interpatient variation.” EX1022, Abstract, 11:27–12:3,

23:9–20. Dr. Bodor himself acknowledged that his oral cladribine formulation in Bodor later became part of “a successful drug.” EX1059, 40:4-8.

17. Drs. Meibohm and Lublin argue that a POSA “would not have been motivated to look to [Bodor] ... to design an oral cladribine dosing regimen” because Stelmasiak’s oral solution had “a higher bioavailability (50%) than Bodor’s 10 mg oral cyclodextrin tablet (39.1–39.4%).” EX2052, ¶83; EX2051, ¶171. Dr. Meibohm’s opinion is unfounded. First, Dr. Meibohm focuses on the purported difference in oral bioavailability between Bodor’s and Stelmasiak’s formulations, whereas a POSA would have also considered formulations’ interpatient variation. Second, Dr. Meibohm fails to acknowledge the recognized advantages that an oral tablet has over a solution formulation, as would be well understood by the POSA. In other words, Dr. Meibohm ignores that Bodor’s solid cladribine tablets had sufficient bioavailability for use in an oral dosing regimen, while further having many other beneficial properties, such as comparatively lower interpatient variability, increased stability, and patient compliance and convenience, as compared to an oral solution like that of Stelmasiak.

18. Drs. Meibohm and Lublin also misrepresent the difference between the oral bioavailability of Bodor’s and Stelmasiak’s cladribine formulations. The prior art reported a *range* of bioavailabilities for oral cladribine solutions, such as that used in Stelmasiak—approximately “37 to 51%.” EX1013, 2; EX1048, 122.

Similarly, Bodor reported a *range* of bioavailabilities for its tablets—between 35.7% and 52.1%. EX1022, 122. Thus, contrary to Dr. Meibohm’s representation of Bodor, a POSA would have understood that Bodor’s tablets have at least comparable bioavailability to prior art oral solutions, such as that of Stelmasiak.

19. A POSA would also have reasonably expected that administering Bodor’s oral cladribine dosage form according to Bodor’s induction dose of 100 to 140 mg (EX1022, 23:15-21) would have resulted in lymphocyte suppression. Bodor’s total oral dose in the induction period is equivalent to a subcutaneous dose of about 0.6 to 0.8 mg/kg for a 70 kg patient. And Rice reported that cladribine administered at a dose of 0.7 mg/kg dose suppressed lymphocytes. EX1018, Abstract. Thus, a POSA would have reasonably expected lymphocyte suppression with Bodor’s dosage form administered at Bodor’s induction dose.

20. Thus, when considered as a whole, the pharmacologist would have advised a POSA who desired to use cladribine to treat MS that Bodor’s tablets were a desirable option for designing a cladribine dosing regimen.

IV. LIST OF DOCUMENTS I CONSIDERED IN FORMULATING MY OPINIONS

21. In formulating my opinions, I considered the following documents:

Exhibit No.	Description
1001	De Luca, G., et al., “Cladribine Regimen for Treating Multiple Sclerosis,” U.S. Patent No. 8,377,903 B2 (filed April 23, 2010; issued February 19, 2013)
1002	Declaration of Aaron Miller, M.D.

Exhibit No.	Description
1013	Stelmasiak, Z., et al., “A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis,” <i>Medical Science Monitor</i> , 4(1):4-8 (1998)
1018	Rice, G.P.A., et al., “Cladribine and progressive MS, Clinical and MRI outcomes of a multicenter controlled trial,” <i>Neurology</i> , 54:1145-1155 (2000)
1022	Bodor, N. and Dandiker, Y., “Oral Formulations of Cladribine,” International Publication No. WO 2004/087101 A2 (filed March 26, 2004; published October 14, 2004)
1024	Schultz, T.W., et al., “Cyclodextrine Cladribine Formulations,” U.S. Patent No. 6,194,395 B1 (filed February 25, 1999; issued February 27, 2001)
1048	Liliemark, J., “The Clinical Pharmacokinetics of Cladribine,” <i>Clinical Pharmacokinetics</i> , 32(2):120-31 (1997)
1050	Chumlea, W.C., “Total body water data for white adults 18 to 64 years of age: The Fels Longitudinal Study,” <i>Kidney International</i> , 56:244-252 (1999)
1059	Transcript of the Deposition of Nicholas S. Bodor. Ph.D. (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
1060	Transcript of the Deposition of Yogesh Dandiker, Ph.D. (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
1061	Transcript of the Deposition of Fred D. Lublin, M.D.
1062	Transcript of the Deposition of Dr. Bernd Meibohm
1064	Albertioni, F., et al., “On the bioavailability of 2-chloro-2'-deoxyadenosine (CdA),” <i>European Journal of Clinical Pharmacology</i> , 44:579-582 (1993)
1065	Kottke, M.K., et al., “Tablet Dosage Forms,” Chapter 10 of <i>Modern Pharmaceutics</i> , 4th Ed., Banker, G.S., et al., eds. (2002)
1066	“Biopharmaceutical Drug Delivery,” BioPharm International (August 1, 2004), accessible at https://www.biopharminternational.com/view/biopharmaceutical-drug-delivery-0 (last accessed February 26, 2024)

Exhibit No.	Description
1067	Brewster, M.E., et al., "Applications of chemically-modified cyclodextrins: use of hydroxypropyl- β -cyclodextrin as an enabling excipient for brain targeting, redox-based derivatives of estradiol, A review of preclinical and clinical findings," <i>Journal of Drug Delivery Science and Technology</i> , 14(1):21-34 (2004)
1068	Davis, M.E., et al., "Cyclodextrin-Based Pharmaceuticals: Past, Present, and Future," <i>Nature Reviews</i> , 3:1023-1035 (December 2004)
1069	Hellriegel, E.T., et al., "Interpatient variability in bioavailability is related to the extent of absorption: Implications for bioavailability and bioequivalence studies," <i>Clinical Pharmacology & Therapeutics</i> , 60(6):601-607 (December 1996)
1070	Leuner, C., et al., "Improving drug solubility for oral delivery using solid dispersions," <i>European Journal of Pharmaceutics and Biopharmaceutics</i> , 50:47-60 (2000)
1071	Martinez, M.N., et al., "A Mechanistic Approach to Understanding the Factors Affecting Drug Absorption: A Review of Fundamentals," <i>Journal of Clinical Pharmacology</i> , 42:620-643 (2002)
1072	Munafo, A., Tran, D., Marcus, S., Ammourey, N., "Pharmacokinetics of oral cladribine (Mylinax) after administration in patients with multiple sclerosis," <i>Serono International S.A., Geneva, Switzerland, Bourn Hall Clinic, Cambridge, UK, Ivax Corp Inc., Miami, USA.</i>
1073	Rajewski, R.A., et al., "Pharmaceutical Applications of Cyclodextrins," <i>Journal of Pharmaceutical Sciences</i> , 85(11)1142-1169 (November 1996)
1074	Saven, A., et al., "Pharmacokinetic Study of Oral and Bolus Intravenous 2-Chlorodeoxyadenosine in Patients With Malignancy," <i>Journal of Clinical Oncology</i> , 14(3):978-83 (March 1996)
1076	Chapters 2, 5, 6, 10 from Shargel, L., et al., <i>Applied Biopharmaceutics & Pharmacokinetics</i> , 4th Ed. (1999)
1077	Loftsson, T., et al., "2-Hydroxypropyl- β -cyclodextrin: Properties and Usage in Pharmaceutical Formulations," <i>PZ Wissenschaft</i> , 136(1):5-10 (January 1991)

Exhibit No.	Description
1078	Sietsema, W.K., "The absolute oral bioavailability of selected drugs," <i>International Journal of Clinical Pharmacology, Therapy, and Toxicology</i> , 27(4):179-211 (1989)
1079	Hermann, R., "The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis," <i>Clinical Pharmacokinetics</i> , 58:283-297 (2019)
2001	MAVENCLAD® (cladribine) Package Insert (2022)
2009	Deposition Transcript of Dr. Aaron Miller (December 12, 2023)
2014	Betaseron® (Interferon beta-1b) Package Insert (1993)
2015	Avonex™ (Interferon beta-1a) Package Insert (1996)
2016	Rebif® (Interferon beta-1a) Package Insert (2003)
2017	Copaxone® (glatiramer acetate) Package Insert (2001)
2018	Novantrone® (mitoxantrone) Package Insert (2000)
2019	Tysabri® (natalizumab) Package Insert (2004)
2043	J. Liliemark et al., On the Bioavailability of Oral and Subcutaneous 2-Chloro-2'-Deoxydenosine in Humans: Alternative Routes of Administration, 10 J. CLIN. ONCOL. 1514 (1992)
2051	Declaration of Fred D. Lublin, M.D.
2052	Declaration of Bernd Meibohm, Dr.rer.nat.
2053	Declaration of Alain Munafo, Ph.D.
2054	Declaration of Nicholas Bodor, Ph.D., D.Sc., d.h.c.
2055	Declaration of Yogesh Dandiker, Ph. D.
2062	J. W. Hainer et al., <i>Dosing in Heavy-Weight/Obese Patients with the LMWH, Tinzaparin: A pharmacodynamic Study</i> , 87 THROMB HAEMOST. 817 (2002) (Excerpt)
2063	B. Meibohm et al., <i>Clinical Pharmacodynamics & Pharmacokinetics</i> , In: R. A. Helms, RA et al. TEXTBOOK OF THERAPEUTICS: DRUG AND DISEASE MANAGEMENT 1 (8th ed. 2006) (Excerpt)

V. THE PERSON OF ORDINARY SKILL IN THE ART ("POSA")

22. I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a

person of ordinary creativity. I also understand that Dr. Miller provided an opinion regarding the level of skill of a POSA in the field relevant to the '947 patent, which I understand to be treating neurological conditions, such as multiple sclerosis (MS). I use the same definition of a POSA. I agree with Dr. Miller that a POSA in this field might rely on, for example, the knowledge and experience of a pharmacologist as part of a multidisciplinary team to determine an appropriate dose for a particular patient. A POSA might also rely on the knowledge and experience of a pharmacologist specializing in formulation sciences as part of a multidisciplinary team to select a suitable formulation of a drug for developing a dosing regimen.

VI. BASIS OF MY ANALYSIS

23. I understand that at issue in these proceedings is the obviousness of claims 36, 38, 39, and 41-46 of the '947 patent. I understand that an obviousness analysis involves determining the scope and content of the prior art, comparing the differences between the claimed invention and the prior art, and resolving the level of ordinary skill in the pertinent art. I understand that Dr. Miller provided an opinion as to these factors, and I do not offer a separate opinion as to the obviousness of the challenged claims.

24. I understand that combining or modifying the teachings of the prior art to achieve the claimed invention is a way to establish obviousness. I understand

that the reason to combine prior art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a person of ordinary skill that does not need to be explicit in any reference. I further understand that even if a prior art reference does not disclose a particular value or range of values, the prior art would still render a claim obvious if it would require only routine experimentation to arrive at the claimed value or range of values. I understand that a particular parameter must first be recognized as a result-effective variable, which I understand is a variable that achieves a recognized result, before the determination of the optimum or workable ranges of the variable may be characterized as routine experimentation. I also understand that the law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the claimed invention.

25. I also understand that where there is a reason to modify or combine the prior art to achieve the claimed invention, there must also be a reasonable expectation of success in so doing. I understand that this does not require absolute predictability of success.

26. I also understand that when considering the obviousness of an invention, one should also consider whether there is any objective evidence that supports the non-obviousness of the invention. This can include: the failure of others; unexpectedly superior results; skepticism followed by praise in the industry; long-felt, but unmet, need; copying; and commercial success.

VII. STATE OF THE ART PRIOR TO DECEMBER 22, 2004

A. Basic Pharmacokinetics Principles

27. Pharmacokinetics (“PK”) is the study of how the body handles a drug after administration, such as the rate and extent of drug absorption, distribution, metabolism, and elimination. EX1076, 30. Drug absorption is the transport of the intact (or unmetabolized) drug from the site of administration to the body’s circulatory system. *Id.*, 99. Three primary factors affect drug absorption: physicochemical properties of a drug (e.g., solubility, permeability), the nature of the drug dosage form (e.g., tablets, solutions), and the route of administration (e.g., oral v. parenteral¹). *Id.* Together, these factors determine the ultimate bioavailability of a drug—a measure of the amount of the drug that reaches systemic circulation and is available at the site of action. *Id.*, 247.

¹ Parenteral refers to intravenous, intramuscular or subcutaneous injection.

EX1076, 108.

28. A common measurement of bioavailability is based on the area under the curve (“AUC”). AUC is the area under the plasma-level vs. time curve, which is equal to the ratio of the amount of unchanged drug reaching the systemic circulation divided by the clearance. *Id.*, 251. The bioavailability obtained from a drug administered in a particular dosage form (e.g., tablet or solution) by a particular route of administration (e.g., oral or parenteral) is typically expressed as a percentage calculated from the comparison of two AUC values. *Id.*, 250. Since the AUC value is a measure of the amount of drug that reached systemic circulation, when the drug is administered by the intravenous (IV) route, 100% of the drug is directly delivered into systemic circulation. *Id.*, 250–251. Therefore, the AUC value obtained from the IV route is the maximum for the amount of drug administered and represents the reference 100% bioavailability. *Id.* A drug product administered by a different route, e.g., oral or by intramuscular (IM) injection, or with a different dosage form, will have its own AUC value. *Id.* The ratio of the AUC value for the non-IV-administered drug product to the AUC from the IV administration, expressed as a percentage, is the bioavailability value. *Id.*, 250.

29. Like any statistical measurement, bioavailability studies typically exhibit variation both between patients (interpatient) and from the same patient receiving multiple administrations over time (inpatient). EX1069, 601. Interpatient and inpatient variations are presented as coefficient of variation

(CV) percentages. *Id.*, 602. Interpatient variation is regularly measured in PK studies and is something that POSAs consider when evaluating dosage forms.

EX1069, 601; EX1048, 3; EX2043, 1514; EX1074, 978; EX1064, 579; EX1022, Tables V, VII.

B. Factors Affecting Drug Bioavailability

30. Before 2004, it was known that various factors affect drug bioavailability. EX1076, 99. The factors included a drug's physicochemical properties (e.g., drug solubility), formulation², and route of administration. *Id.* I explain how each of these factors would affect bioavailability of a given drug below.

31. Drug solubility (i.e., the maximum concentration of the drug that can be completely dissolved in a liquid solution system) is “a key determinant of its oral bioavailability.” EX1070, 47; EX1071, 620. With slightly water soluble drugs, such as cladribine, having such drugs “dissolved in a carrier with relatively

² It is common in the field, although not technically correct, to refer to formulation and drug dosage form interchangeably. In this declaration I will refer to formulation as the composition, that is, the active drug substance plus excipients, and a dosage form as the form the formulation is presented for administration to the patient (tablet, capsule, etc.).

good aqueous solubility are of particular interest as a means of improving oral bioavailability.” EX1070, 48. Cyclodextrins, which I discuss below, were known to be one such carrier before 2004. *Id.*, 53; EX1059, 95:11–96:1, 104:2–16; EX1068, 1127.

32. The formulation of a drug also affects absorption, and therefore bioavailability. EX1076, 99. Dr. Meibohm admitted this much, stating that “[b]ioavailability is usually a pharmacokinetic property that’s specific for a formulation,” and that “the absorption rate constant” is specific for a formulation. EX1062, 42:8–43:16. A drug “formulation” includes “the active drug substance and selected ingredients (excipients) that make up the dosage form.” EX1076, 129. Examples of dosage forms include tablets, capsules, solutions (for oral or parenteral administration), sachets, mucoadhesive forms, etc. *Id.*

33. The route of administration also affects drug bioavailability. Dr. Meibohm agreed, stating that the “route of administration ... may determine the bioavailability.” EX1062, 50:1–6. Oral routes generally have a lower bioavailability than both IV and subcutaneous injections. *Id.*; EX1076, 109–111. But solid dosage forms can result in high oral bioavailability for poorly water-soluble drugs if the drug is dissolved in a carrier with comparatively good aqueous solubility. EX1070, 48. Cyclodextrins (CDs) are an example of such a carrier that can increase solid solubilization of poorly soluble drugs. *Id.*

C. Before 2004, It Was Known That Oral Bioavailability Can Vary Without Compromising the Effectiveness of a Drug.

34. While oral bioavailability was a consideration for a POSA before 2004, there was no minimum bioavailability that was required, and drugs having wide range of oral bioavailability would still be successful. Indeed, “poor oral bioavailability will not compromise the effectiveness of a drug if it is possible to deliver consistent efficacy without increasing the risk of an unacceptable adverse reaction.” EX1078, 193, Table 1. Dr. Meibohm conceded that the “absolute minimum” for bioavailability is zero percent, and that “[t]here are examples of approved drugs with a bioavailability of 1 to 2 percent.” EX1062, 59:3–14. Dr. Bodor testified that although “the objective” for his oral cladribine formulation was “to achieve more than 30 percent bioavailability,” he set a threshold of “10 percent or so percentage of bioavailability” at which the drug “cannot be [] successful.” EX1059, 39:1–18. Dr. Bodor’s³ testimony that his bioavailability goal of 30% for a

³ Upon review of Dr. Bodor’s CV (EX2054), I would characterize him as someone with extensive experience in the field of pharmaceuticals and an accomplished inventor, as Dr. Meibohm conceded (“Q: So you considered Dr. Bodor to be an expert and an inventor in pharmaceuticals, is that right? A: That was how he was always characterized to me.” EX1062, 72:12-15; “Q: And was Dr. Bodor

cladribine tablet being known “generally in the field” is representative of pharmacologists in the art before 2004. EX1059, 40:14–17.

35. Indeed, before 2004, there were plenty of known commercial drugs with a wide range of oral bioavailability, from the single digits to almost 100% AUC. EX1078, Table 1. The following table demonstrates such variability for other commercial solid dosage forms prior to 2004 (*id.*):

Solid Oral Drug	Absolute Oral Bioavailability
Acebutolol [Sectral]	37%
Biperiden [Akineton]	33%
Doxepin [Silenor]	13–45%
Mebendazole [Vermox]	22%
Omeprazole [Prilosec/Losec]	25–100%
Penicillin G	15–30%

36. Thus, there was a wide range of acceptable oral bioavailability known in the art before 2004.

characterized as an expert and inventor in pharmaceuticals as of the 2004 time frame? A: Well, he was characterized in 1997, so I assume that continued.” *Id.*, 73:4-8).

D. Pre-2004 Art Expressed Preference for Formulations With Lower Interpatient Variability.

37. Interpatient variability is another factor that pharmacologists take into account when developing new drug candidates—generally, the lower, the better.

Lower interpatient variability is a desirable quality for several reasons.

38. *First*, when a given formulation shows a large variability in bioavailability, it is far more difficult to accurately prescribe a dose to reach a desired systemic concentration. EX1069, 605. Because “[t]he drug product must effectively deliver the active drug ... so that the intended therapeutic effect is achieved” (EX1076, 151), having a wide variation in systemic concentration due to large interpatient variability of bioavailability results in a drug that is not as clinically effective as a drug with a smaller interpatient variability. Dr. Bodor agrees with me: when “one patient shows 10 percent, the other 50 percent [this] cannot be a successful drug because the variability by this patient who is treated is too much, you cannot assure the desired blood concentration.” EX1059, 41:1–4. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

39. *Second*, having lower interpatient variability also decreases the risk of unexpected toxicity. EX1069, 605. Formulations with high coefficient of variation

(CV) values “are the products for which the results of the bioavailability studies and even previous clinical experience are less likely to apply to a new patient.” *Id.*

40. Thus, having a low interpatient variability was known to be beneficial for a formulation.

E. Before December of 2004, Solid Oral Dosage Forms Were Preferred over Liquid Dosage Forms.

41. Before December 2004, solid oral formulations had been described as a “Holy Grail” for drug formulators. EX1066, 5. This is because “[o]ral administration [] simplif[ies] the treatment for both patient and physicians” and has the advantage of convenience, decreased cost of administration, safety, and patient comfort. EX1076, 154–155; EX1064, 581. Parenteral administration, on the other hand, often required medical personnel to administer the drug, involves patient discomfort during injection, and has a higher overall burden of administration. EX1065, 287; EX1022, 2:9–19. By 2002, “well over 80% of the drugs in the United States that are formulated to produce systemic effects are marketed as oral dosage forms.” EX1065, 287. I understand that Dr. Miller testified that oral delivery of drugs enhanced patient compliance because they alleviated repeated doctor visits, or the discomfort of injections. I agree—as did Drs. Bodor, Dandiker, and Meibohm: “People [would] rather take a pill than get injected;” (EX1059, 59:9–60:14); “With an oral formulation ... it gives the patient the ability to dose themselves at the right and the appropriate time. ... [It] is just better for the

patient;” (EX1060, 49:5–13); “[S]ome dosage forms are easier to use than others.

... If I have a subcutaneous injection that requires training by the patient, if it’s self-administered, and intravenous administration would require a visit to a healthcare provider; whereas, an oral administration of a tablet is done by the patient themselves.” (EX1062, 50:11–52:9).

42. Among oral dosage forms, tablets are the most common solid oral dosage forms, and described as “the manufacturer’s dosage form of choice because of their relatively low cost of manufacture, package, and shipment; increased stability and virtual tamper resistance.” EX1065, 287. Dr. Bodor conceded that tablets have increased stability especially when compared to liquids or liquid capsules. *Id.*; EX1059, 61:18–62:14 (Dr. Bodor states “[a] molecule, which is a drug, can undergo degradation. And if it’s in a solution, it’s more likely to degrade than if it’s in a solid form. In a solid form, it’s more stable.”). Tablets also are more profitable to manufacture and have increased shelf life. *Id.*; EX1067, 23; EX1077, 9, Table 3. Thus, a POSA generally would have preferred and sought a tablet over other available dosage forms.

F. Before 2004, Cyclodextrins Were Known to Increase Oral Bioavailability, Stability, and Solubility of Drugs.

43. Before 2004, POSAs used cyclodextrins (“CD”) as complexing agents to increase the aqueous solubility of drugs in order to increase their oral bioavailability and to improve stability. EX1068, 1027 (“Cyclodextrins (CDs) can

be used to achieve the following: [e]nhance solubility, [e]nhance bioavailability [and] [e]nhance stability ...”). Dr. Meibohm conceded this fact. EX1062, 69:10–21 (“Q: Now, how is it exactly that cyclodextrins work to increase bioavailability of a drug? ... A: As far as I understand, cyclodextrins solely increase – get more drug into solution, and by that, as a secondary effect, increase bioavailability. Q: And this understanding regarding cyclodextrins and their role in solubility and bioavailability, is that something you were aware of in the 1990s? A: Yes.”).

44. Before 2004, the benefits of CDs in oral drug delivery were well known, including “increasing drug bioavailability through an increase in apparent rate and extent of drug dissolution,” “increasing drug stability or release time,” “decreasing local tissue irritation” and “masking of objectionable taste.” EX1073, 1150. The observed increases in oral bioavailability were “predominantly [a] result from increases in the apparent solubility of the drug.” *Id.* Cyclodextrins have a unique three-dimensional cavity shape that allows a poorly-soluble “guest” molecule to reside and solubilize in an aqueous environment, referred to as the “inclusion complex.” EX1068, 1023–1025.

45. One widely used cyclodextrin before 2004 was hydroxypropyl- β -cyclodextrin (“HP- β -CD”), the cyclodextrin species described in Bodor (EX1022, 13:16) and used in the MAVENCLAD® formulation (EX2053, ¶26). HP- β -CD improved the clinical usage of the drugs “by increasing their aqueous solubility,

rate of dissolution and pharmaceutical availability” while lacking toxicity seen in other CD species. EX1077, 8–9, Table 2. And before 2004, Schultz showed a linear relationship between increasing HP- β -CDs and increasing solubility of cladribine. EX1024, 7:19-43 (Example 2).

46. Beyond enhancing solubility and oral bioavailability, pharmacologists utilized CD to enhance drug stability, both *in vivo* and on the shelf. EX1073, 1150; EX1077, 9; Table 3. Once consumed, CD’s can improve the stability of a formulation passing through gastrointestinal transit to mediate modified (more controlled) release and delivery. EX1073, 1150. The cyclodextrin inclusion complex is able to protect drugs from being chemically degraded through first-pass metabolism⁴ before entering systemic circulation. *Id.*

47. Cyclodextrins were also used to increase the stability of a product before administration by increasing the shelf-life of a product. “[T]he rate of degradation of a drug within the inclusion complex is slower than out in the solution” and adding HP- β -CD to an aqueous solution of a drug “results in increased stability and thus, longer shelf-life.” EX1077, 9, Table 3. The increased shelf life was thought to be a result of the inclusion complex of cyclodextrins being

⁴ Presystemic elimination (i.e., the metabolism of drug molecules before it reaches systemic circulation). EX1076, 153.

able to protect guest molecules against hydrolytic and oxidative instabilities:

“[c]onvenient formulation [is complicated] due to the poor water solubility ... as well as its hydrolytic and oxidative instabilities. ... These complexes [HP- β -CD] act to both increase the water solubility ... as well as to significantly increase [] shelf life.” EX1067, 23.

G. Oral Solid and Oral Liquid Dosage Forms of Cladribine Were Known in the Art Before December of 2004.

48. Consistent with the general preference of oral over parenteral drug administration, the art described oral dosage forms of cladribine before 2004. Both oral liquids and oral solid formulations of cladribine were known in the art. EX1048, 122 (“The oral bioavailability in these trials varies from 37 to 51% when the saline solution for intravenous administration is given to patients to drink.”); EX1013, Abstract, 5 (“The drug was prepared as sterile solution in isotonic saline”); EX1074, 978 (“[A] phosphate-buffered solution of 2-CdA”); EX2043, 1514 (“Ten patients were administered CdA orally that was dissolved in phosphate-buffered saline (PBS)”); EX1064, 579 (“A solution [] of CdA in saline [] was prepared”); EX1024, 2:24-25 (“There is provided by the present invention a solution of cladribine in water”).

49. For example, in early trials with oral cladribine, patients were given a solution previously used for intravenous administration as a drink. EX1048, 122; EX1013, Abstract; EX2043, 1514; EX1074, 978; EX1064, 579. The solution was a

simple phosphate-buffered saline (PBS) solution of cladribine. EX2043, 1514; EX1074, 978; EX1064, 579.

50. The prior art also reported on the bioavailability of oral cladribine solutions. For example, Albertioni measured the pharmacokinetics of an oral cladribine solution in four patients and reported the bioavailability of “42% after food intake” and “46% while fasting.” EX1064, Abstract, Table 2. Albertioni also noted an interpatient variability of 0.26 after food intake and 0.27 while fasting. *Id.* I note that this is the lowest interpatient variability achieved in the prior art for cladribine solutions. Liliemark reported a bioavailability of $48\% \pm 8\%$ for a 0.14 mg/kg dose and $55\% \pm 17\%$ for a 0.28 mg/kg dose. EX2043, Abstract, Table 1, FIG. 1. Liliemark’s interpatient variability was 0.29 and 0.44, respectively, reporting an average of 0.38. *Id.*, Table 1, 1516. Similarly, Saven reported an oral bioavailability of cladribine oral solution to be 37%, with interpatient variability of 41.6%. EX1074, Abstract, Table 3. Stelmasiak, citing to Liliemark, reported that its dosing regimens produced “equivalent area under the concentration-time curve of the drug” (~50% bioavailability), although Stelmasiak did not conduct any pharmacokinetic studies. EX1013, 5. Thus, a POSA would interpret Stelmasiak as referring to the prior art for oral bioavailability of cladribine solutions.

51. Liquid oral formulations of cladribine had known shortcomings. Cladribine had limited stability in a simple saline solution, which resulted in acid-

catalyzed hydrolysis. EX1024, 1:44-51. The acidic environment of the stomach caused particular issues: “[u]se of the compound orally has been limited by the fact that cladribine is acid labile and would not be stable in the acidic environment of the gastro-intestinal system.” *Id.* Liquid formulations also had “limited shelf-life stability.” *Id.*

52. In 1999, Schultz reported a solid dosage form of cladribine, stabilized by cyclodextrins. *Id.*, 1:4-10. Schultz reported that cladribine was significantly more soluble in aqueous media when formulated with cyclodextrin. *Id.*, Table 2. The cladribine formulation was also “significantly more stable against hydrolysis when combined with cyclodextrins,” which was “of particular benefit in the formulation of solid oral dosage forms, where the compound would normally undergo hydrolysis in the acid pH of the stomach contents.” *Id.*, 5:29-34.

53. In 2004, Bodor disclosed a solid cladribine form “especially suited for the oral administration of cladribine.” EX1022, Abstract. Bodor’s dosage forms, e.g., tablets, included “an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex,” and it described the intimate amorphous admixture as a “complex cladribine-cyclodextrin complex.” *Id.*, 5:8–13.

54. Bodor reported the oral bioavailability of its cladribine tablets to be higher than previous oral cladribine dosage forms. According to Bodor, the relative⁵ bioavailability of a 3 mg tablet was 43.1% (35.7% lower limit and 52.1% upper limit⁶). *Id.*, Table VI. Absolute⁷ bioavailability of a 10.0 mg tablet was 39.1% with a lower limit of 35.9%. *Id.*, Table VIII. The absolute bioavailability of the 3.0 mg tablet was 34.0% with a 31.2% lower limit. *Id.* Based on these data, Bodor concluded that its complex “improved cladribine absorption, as reflected by higher bioavailability and/or lower interpatient variation.” EX1022, 12:1–3. Dr. Bodor conceded the same during his deposition. EX1059, 38:18–39:4, 103:3–6 (“Q: Dr. Bodor, do you stand by the disclosures of your Bodor PCT application? A: Yes. Yes. Yes.”), 41:16–42:7 (“[I]f you look in the patent, we have done a very important demonstration of the reduction of the interpatient variability.”). Merck’s

⁵ Relative bioavailability is the availability of a drug from a drug product as compared to a recognized standard. EX1076, 250.

⁶ Calculated using standard deviation.

⁷ Absolute bioavailability is the systemic availability of a drug after extravascular (e.g., oral, rectal, transdermal, subcutaneous) administration, and is measured by comparing the respective AUCs after extravascular and IV administration. EX1076, 250.

MAVENCLAD® marketed product is based on Bodor's tablets containing this complex cladribine-cyclodextrin complex. EX2053, ¶26.

VIII. MY UNDERSTANDING OF HOPEWELL'S OBVIOUSNESS ARGUMENT

55. I understand that Hopewell and Dr. Miller argued that claims 36, 38, 39, and 41-46 would have been obvious over the combined teachings of Bodor and Stelmasiak. I do not provide an opinion on the obviousness of the challenged claims, but my understanding of the argument is summarized below.

56. Bodor teaches "compositions of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine." EX1022, Abstract. According to specification, "[o]ral delivery of drugs is often preferred to parenteral delivery for a variety of reasons, foremost patient compliance, or for cost or therapeutic considerations." *Id.*, 2:9–11. Bodor further teaches that cladribine formulated into the described solid oral dosage forms is in "a high thermodynamic state," which results in "improved cladribine absorption, as reflected by higher bioavailability and/or lower interpatient variation." *Id.*, 11:27–12:3, 23:9–20.

57. Stelmasiak reports the results of a clinical study in which 10 "patients with the remitting-relapsing form of MS" were treated with cladribine. EX1013, Abstract. Stelmasiak discloses that the oral cladribine "was prepared as [a] sterile solution in isotonic saline, 1 mg/ml." *Id.*, 5. Stelmasiak reports the bioavailability of the solution to be about 50% (citing to Liliemark for the actual measurement,

EX2043). *Id.* Stelmasiak concludes that “[i]n patients with remitting-relapsing multiple sclerosis treatment with cladribine decreases lymphocyte counts in peripheral blood, to 1/3 of the initial values on average.” *Id.*, 7.

58. I understand that according to Dr. Miller, a POSA would have had a reason to treat MS with oral cladribine tablets by modifying Bodor’s oral cladribine regimen to re-treat a patient with another course of cladribine, as taught by Stelmasiak, because MS is a chronic, progressive disease that typically requires periodic treatment and cladribine’s therapeutic effects are impermanent. I also understand that Dr. Miller opined that it was routine in the art to monitor a patient’s lymphocyte counts when treating a patient with an immunosuppressant such as cladribine, and a POSA would have arrived at the claimed maintenance period dose and length by routine optimization. I also understand that Dr. Miller concluded that a POSA would have a reasonable expectation of success by treating MS with Bodor’s oral dosage form following an induction period, a cladribine-free period, a maintenance period, and a cladribine-free period, because oral cladribine had previously been shown to have clinical efficacy in patients with MS using cyclical treatment/no treatment regimens.

59. I have been asked to provide an opinion as to whether a pharmacologist would have advised a POSA who wanted to use cladribine to treat

MS that Bodor's tablet would be a desirable choice for use in a cladribine dosing regimen.

IX. A POSA WOULD HAVE SELECTED BODOR'S TABLETS CONTAINING COMPLEX CLADRIBINE-CYCLODEXTRIN COMPLEX TO DESIGN AN ORAL CLADRIBINE REGIMEN.

A. A POSA Would Have Recognized That Bodor's Tablets Had More Overall Benefits Than Did Oral Solutions.

60. A POSA prior to December 22, 2004, would have used Bodor's oral cladribine tablets for use in an oral cladribine regimen because Bodor's tablets had a host of benefits, such as an acceptable bioavailability, lower interpatient variability, increased stability, and greater potential for patient compliance and convenience than other cladribine dosage forms. Furthermore, like I explained above, manufacturers preferred tablets over other dosage forms for their low cost of manufacture, package, and shipment. EX1065, 287. Tablets are also more stable than liquids or liquid capsules. *Id.*; EX1059, 61:18–62:14. Thus, they are more profitable to manufacture and have increased shelf life. *Id.*; EX1067, 23; EX1077,

61. Bodor described its "complex cladribine-cyclodextrin complex" as being "an intimate amorphous admixture." EX1022, 8:17–19. A POSA advised by a pharmacologist would have appreciated that an amorphous solid exhibits a substantially higher rate and extent of dissolution of a drug compared to its crystalline counterpart. EX1070, 49. As I explained above, increasing the solubility

of a drug, especially a poorly soluble drug like cladribine, often increases the oral bioavailability of the drug. EX1073, 1150.

62. A POSA also would have had no reason to disregard (indeed, a POSA would have strong reasons to accept) Dr. Bodor's explicit statements in Bodor—namely, that his “solid oral dosage form” provided “improved bioavailability” and “lower interpatient and/or inpatient variation following administration,” and that his complex cladribine-cyclodextrin complex was “well-suited for optimizing the oral bioavailability of cladribine.” EX1022, 8:22–30. I explained Dr. Bodor's reputation in the field before 2004 in ¶34, Footnote 3, as an accomplished inventor with extensive experience in the field of pharmaceuticals. A POSA would not have disregarded Dr. Bodor's statements regarding his oral cladribine formulation. For example, I note that Dr. Munafo characterized a 35–39% bioavailability range for cladribine as a “favourable pharmacokinetic profile[.]” EX1072, Abstract.

63. Consistent with this principle that was well-known by 2004, Dr. Dandiker confirmed that he and Dr. Bodor made the cladribine formulation disclosed in Bodor amorphous (and thus, more soluble) to “increase bioavailability.” EX1060, 157:16–158:2. And Dr. Bodor conceded that Bodor shows that the disclosed tablets achieved “high blood levels” of cladribine. EX1059, 38:18–39:4 (“Q: Did you achieve the high blood levels of cladribine with your complex cladribine-cyclodextrin complex described in your Bodor PCT

application? A: Well, it is in the patent, so you can see the results compared to injectable forms. You can achieve more than 30 percent, that was the objective, to achieve more than 30 percent bioavailability, and you ... can read the report, something like 39 or so percent.”). And, Dr. Bodor admits that generally in the field, “achieving at least 30 percent bioavailability” makes it practical to have an oral formulation, making Bodor’s tablets “a successful drug.” *Id.*, 38:18-40:17. Thus, a POSA would understand that the bioavailability of Bodor’s dosage form was acceptable for a cladribine formulation.

64. Bodor also emphasizes the lowered interpatient variability achieved with the tablets. EX1022, 5:5–7 (“This product is a complex cladribine-cyclodextrin complex, and the solid oral dosage form containing it improves oral bioavailability and/or achieves lower interpatient and/or inpatient variation of the drug.”). As I explained above, interpatient variability is an important measurement because POSAs need to have confidence that prior bioavailability studies will be accurate for an individual patient, and the lower the interpatient variability, the better. I have prepared the following table to compare the interpatient variability of cladribine solutions in the prior art with Bodor (EX1022, Tables V, VII; EX1013, 2; EX1074, Abstract; EX1064, 579):

Prior Art	Interpatient Variability (CV ⁸)	Dosage Form
Bodor	28–30%	Tablet
Stelmasiak (citing Liliemark 1992)	38%	Oral Solution
Saven	40%	Oral Solution
Albertioni	26–27%	Oral Solution

65. Because Bodor’s tablets have reportedly lower interpatient variability than most oral solutions, a POSA would have had a reason to use Bodor’s formulation to develop oral cladribine dosing regimen.

66. POSAs would have also preferred Bodor’s tablet over an oral solution because it was well known in the art that solid oral delivery is preferable over liquid formulations. EX1065, 287. As I explained, solid oral formulations are the “Holy Grail” for formulators. EX1066, 5. Tablets generally have an increased stability and shelf-life when compared to liquids or liquid capsules. EX1065, 287. They are also less expensive to manufacture, more profitable, and tamper resistant. *Id.* A pharmacologist thus would have advised a POSA that a tablet would be the preferable mode of drug delivery.

⁸ Coefficient of Variation. ¶29.

67. Contrary to Drs. Meibohm and Lublin's opinion, a POSA would consider more factors than just bioavailability when evaluating the benefits of a particular formulation and dosage form. Drs. Meibohm and Lublin concluded that "a POSA ... would not have been motivated to look to combine/modify Bodor and Stelmasiak" because Bodor teaches a formulation "having lower bioavailability compared to Stelmasiak's formulation." EX2052, ¶21; EX2051, ¶171. But Drs. Meibohm and Lublin's view is too narrow, hence curtailing both the problem and the solution. A POSA would not be so short-sighted as to limit themselves to only consider a single factor (bioavailability) in developing a drug product, but rather would have taken the needed holistic approach in selecting a formulation and dosage form. A pharmacologist would have advised a POSA to consider all the important parameters, patient convenience, the shelf-life of a formulation, and interpatient variation.

B. Drs. Meibohm and Lublin Misleadingly State That Stelmasiak's Oral Solution of Cladribine Had Higher Bioavailability Than Bodor's Tablet.

68. A POSA would not have concluded that Stelmasiak's oral cladribine solution had a higher bioavailability than Bodor's oral cyclodextrin-complex tablet. Drs. Meibohm and Lublin state that a POSA "would have understood that Stelmasiak's oral PBS solution and dosing method reported a higher bioavailability

(50%) than Bodor's 10 mg oral cyclodextrin tablet (39.1–39.4%).” EX2052, ¶83; EX2051, ¶171. But their statements are misleading.

69. Dr. Meibohm does not dispute that Stelmasiak did not report measuring oral bioavailability of the solution. EX2052, ¶¶56, 83. Instead, Dr. Meibohm agrees that Stelmasiak cites to Liliemark (EX2043) for this teaching. *Id.*, ¶56. Dr. Lublin agrees with Dr. Meibohm's opinion that “Stelmasiak's formulation has 50% bioavailability.” EX2051, ¶168. Dr. Meibohm fails to note, however, that the prior art was not limited to Liliemark's 1992 publication. I've prepared the following table based on the prior art to compare the prior art to other references in the art by Liliemark (EX1013, 2; EX1048, 3):

Petitioner's References	Bioavailability
Stelmasiak (EX1013, 2).	48, 55% ⁹ (“approximately 50%”)
Liliemark (1997) (EX1048, 3).	37–51%

70. Exhibit 1048 cites additional art that discloses similar bioavailability values for oral cladribine solutions (EX2043, Abstract; EX1064, Abstract, Table 2; EX1074, Abstract, Table 3):

⁹ Stelmasiak reports AUC by reference to Liliemark (EX2043). EX1013, 2 (“These dosing regimens produce equivalent area under the concentration time curve of the drug.”).

Prior Art	Bioavailability
Liliemark 1992	48, 55% (“approximately 50%”)
Albertioni	42, 46%
Saven	37%

71. Further, Liliemark overestimated the oral bioavailability of the cladribine solution. Indeed, according to Saven, Liliemark’s “higher” bioavailability values “could be due to residual drug from previous dose(s).” EX1074, 982. As Saven explained, “[t]he F values reported here (~37%) are lower than those reported by Liliemark et al (~55%), who gave [cladribine] as a 2-hour IV infusion, subcutaneous injection, and an oral dose over 3 consecutive days ... with no washout periods between drug administrations.” *Id.* Washout periods are necessary because they ensure that most of a drug has been eliminated from the body before administering a new dosage (thus avoiding double counting a portion of the drug). EX1076, 263. And Liliemark’s (and therefore Stelmasiak’s) bioavailability values were measured without the washout periods, and therefore likely overinflated. EX1013, 2; EX2043, Abstract. Bodor, on the other hand, separated the treatment days “by a drug-free interval of at least 5 days.” EX1022,

33:10-39:18 (Examples 4, 5).¹⁰ A POSA would have understood Bodor's bioavailability values to be more accurate than Liliemark's overinflated values because the effect of drug accumulation due to lack of washout in the systemic circulation with Bodor's dosage form would be lessened.

72. Dr. Meibohm also focuses on the absolute bioavailability of only Bodor's 10 mg tablet in Table VIII of EX1022, which discloses a dose normalized absolute oral bioavailability of 39.1%, measured as the area under the curve for the measured data from zero extrapolated to infinity (AUC_{inf}):

TABLE VIII

Ratios of Oral to I.V. Pharmacokinetic Parameters and Corresponding Lower Limit (LL) for the one-sided 95% Confidence Interval for Cladribine Study (n=26)

Pharmacokinetic Parameter	Oral Administration			
	3.0 mg		10.0 mg	
	Ratio*	LL	Ratio*	LL
AUC_{inf}	34.5	31.7	39.1	35.9
AUC_t	34.0	31.2	39.4	36.1

*Ratios (dose normalized) and Corresponding 95% LL obtained via inverse transformation of log-transformed data.

¹⁰ The half-life of Bodor's cyclodextrin-cladribine tablet ranged from 5.6 to 7.55 hours. EX1022, Table V, Table VII. Thus, five days was more than ten half-lives, which is a typical washout period length. EX1076, 263.

EX1022, Table VIII (annotated).

73. But Dr. Meibohm does not consider the entire teaching of Bodor.

Because Bodor's values were dose normalized (i.e., the differences in bioavailability between the dosage amounts of 3.0 mg and 10.0 mg was accounted for), a POSA would not pick and choose, but would have also considered Table VI. Table VI discloses that the dose normalized oral bioavailability of Bodor's cladribine ranged from 35% to 52.1%:

TABLE VI

Ratios of Oral to Subcutaneous Pharmacokinetic Parameters and Corresponding Two-Sided 90% Confidence Intervals for Cladribine Study (n=12).

Pharmacokinetic Parameter	3 mg Tablet 1		3mg Tablet 2		3mg Capsule	
	Ratio*	LL, UL	Ratio*	LL, UL	Ratio*	LL, UL
AUC _{inf}	43.1	35.7, 52.1	38.4	31.8, 46.4	38.9	32.1, 47.0
AUC _t	41.9	34.6, 50.8	37.2	30.7, 45.0	37.6	31.0, 45.5

*Ratios (dose normalized) and Corresponding 95% LL obtained via inverse transformation of log-transformed data.

EX1022, Table VI (annotated).

74. A POSA would have also considered Table VI along with Table VIII of Bodor because the intravenous injection and subcutaneous routes of administration for cladribine have equal bioavailability. EX1048, Summary ("The

oral bioavailability of cladribine is 37 to 51%, and that of subcutaneous administration is 100%). As I explained above, intravenous injection has a 100% bioavailability, so cladribine is an unusual drug in that there is no difference between absolute bioavailability (where intravenous injection is always the reference AUC) and subcutaneous administration, and thus relative bioavailability using subcutaneous administration as the reference AUC is the same as absolute bioavailability.

75. A POSA would have compared Bodor's range of Table VI to the reported bioavailability of oral cladribine solution:

2.1 Oral Administration

There are 4 reports on the oral bioavailability of cladribine.^[29-32] The oral bioavailability in these trials varies from 37 to 51% when the saline solution for intravenous administration is given to patients to drink.^[29,30,32] Thus, when administered

EX1048, 3 (annotated).

76. The "37 to 51%" range is supported by the studies above: Saven, Albertioni, Stelmasiak, and the 1992 Liliemark publication. *Id.* Thus, it captures the prior art. And a POSA would have understood that the absolute oral bioavailability of Bodor's tablets and of Stelmasiak's oral solution are at least comparable. The difference between Bodor's 35.7–52.1% range and the prior art (and thus Stelmasiak's) 37–55% range is insignificant.

77. The insignificance in the variability in bioavailability measurements are demonstrated in the following example. Munafo's later measurement of Bodor's same cladribine cyclodextrin complex was 45.6%. EX1079, 285. Since these two formulations are the same, with substantial variation between the two bioavailability measurements, it demonstrates that bioavailability measurements have inherent variability. And while Munafo's study was post-filing, it further shows that Stelmasiak and Bodor have similar bioavailability.

X. A POSA WOULD HAVE HAD A REASONABLE EXPECTATION THAT BODOR'S TABLET AND DOSES WOULD SUPPRESS LYMPHOCYTES.

78. I understand that Dr. Miller testified that a POSA would have reasonably expected the claimed cumulative dose of cladribine to treat MS. Drs. Meibohm and Lublin argue that because Bodor "teaches a lower cumulative dosage (100-140 mg) in the initial dosing phase, and reports lower oral bioavailability than Stelmasiak," a POSA would have no reason to believe that using Bodor's lower cumulative dose "would have been effective or successful in treating multiple sclerosis." EX2052, ¶¶85-88; EX2051, ¶¶150, 158, 167. While I do not offer an opinion as to POSA's expectations vis-à-vis cladribine's treating MS, it is my opinion that a POSA would have reasonably expected that administering Bodor's oral cladribine dosage form according to Bodor's cumulative induction dose would have resulted in lymphocyte suppression.

79. A POSA would have reasonably expected a lymphocyte suppression with Bodor's cumulative dose because Rice disclosed that cladribine suppressed the mean lymphocyte count when administered at a dose comparable to that of Bodor's. EX1018, 1145–46. Specifically, Rice disclosed that cladribine was administered subcutaneously at a dose of, e.g., “0.07 mg/kg/day for 5 consecutive days every 4 weeks” for two cycles (“total dose, 0.7 mg/kg”). *Id.*, Abstract. According to Rice, at this dose of cladribine “[t]he mean lymphocyte count was suppressed ... from the first cycle of treatment throughout the double-blind observation phase.” *Id.*, 1152.

80. As explained, Bodor teaches administering “10 mg of cladribine ... once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment.” EX1022, 23:15–20. I understand that Dr. Miller explained that a POSA would have understood that the two months of administration constitute an “induction dose.” And, as I understand that Dr. Miller further explained, and I agree, Bodor's induction dose was 100 mg to 140 mg. For an average weight patient, the induction dose equals 1.4 – 2 mg/kg (100 mg (or 140 mg) divided by 70 kg).

81. A POSA, as advised by a pharmacologist, would have understood that Bodor's oral dose, corrected for its bioavailability (about 40%), is the dose (in

mg/kg) x 0.4 (i.e., 40% bioavailability). EX1022, Table VI. This is equivalent to a subcutaneous dose of about 0.6 to 0.8 mg/kg (bioavailability of about 100%; EX1048, Summary):

$$\text{Equivalent subcutaneous dose} = 1.4 \frac{\text{mg}}{\text{kg}}^{11} \times 0.4 = 0.56 \frac{\text{mg}}{\text{kg}}$$

$$\text{Equivalent subcutaneous dose} = 2.0 \frac{\text{mg}}{\text{kg}}^{12} \times 0.4 = 0.8 \frac{\text{mg}}{\text{kg}}$$

82. The 0.6 to 0.8 mg/kg dose is very similar to Rice's 0.7 mg/kg dose. EX1018, Abstract. And because Rice's 0.7 mg/kg dose caused a lymphocyte suppression, a POSA would have reasonably expected Bodor's 0.6 to 0.8 mg/kg dose also to suppress lymphocytes to a similar level as Rice's dose.

83. In conclusion, a pharmacologist would have advised a POSA who desired to use cladribine to treat MS to select Bodor's tablets. They would have done so because tablets bring a host of benefits, and Bodor's oral bioavailability was at least comparable to the prior art's oral solutions, such as Stelmasiak's with lower interpatient variability. A POSA would have also had a reasonable

¹¹ Using the average adult weighing about 70 kg (EX1050): $100 \text{ mg} \div 70 \text{ kg} = 1.4 \text{ mg/kg}$.

¹² Using the average adult weighing about 70 kg (EX1050): $140 \text{ mg} \div 70 \text{ kg} = 2.0 \text{ mg/kg}$.

expectation of success that Bodor's induction dose would have suppressed lymphocyte counts.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of title 18 of the United States Code.

Date: 04/03/2024



Dr. Rodolfo Pinal, Ph.D.