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 IPR2023-00480
Patent 7,713,947

Case IPR2023-00481
Patent 8,377,903

DECLARATION OF ALAIN MUNAFO, Ph.D.

MERCK 2053
HOPEWELL v MERCK
IPR2023-00481

I, Alain Munafo, Ph.D., declare as follows:

I. INTRODUCTION

1. I am over eighteen years of age, and I am competent to testify as to the matters set forth herein if I am called upon to do so.

2. I submit this Declaration on behalf of Merck Serono S.A. ("Patent Owner") for consideration by the Patent Trial and Appeal Board in the following *Inter Partes* Review proceedings: IPR2023-00480 ("'480 IPR") and IPR2023-00481 ("'481 IPR"). I understand that the '480 IPR corresponds to *Inter Partes* Review of U.S. Patent No. 7,713,947 ("the '947 patent") ('480 Ex. 1001) and the '481 IPR corresponds to *Inter Partes* Review of U.S. Patent No. 8,377,903 ("the '903 patent") ('481 Ex. 1001).

3. I am being compensated for my time in preparing this declaration at my usual consulting rate of 450 Swiss Francs per hour. My compensation is in no way contingent on the substance of my testimony or the outcome of this or any other proceeding.

4. I am a named co-inventor of both the '947 patent and the '903 patent. When U.S. Provisional Application No. 60/638,669 and European Provisional Application No. EP04106909, to which the '947 patent and the '903 patent claim priority, were filed on December 22, 2004, and for more than two years before

then, I was working with other co-inventors of the ’947 patent and the ’903 patent to design and develop an oral dosing regimen for cladribine.

5. I am providing this declaration as a co-inventor of the ’947 patent and the ’903 patent and as someone knowledgeable about the relationship and joint research and development agreement between the teams at Serono[1] and IVAX.[2]

6. I have reviewed a copy of PCT Application WO 2004/087101 (“Bodor PCT”) which was provided to me by counsel. I understand it is numbered Ex. 1022. The Bodor PCT names Drs. Bodor and Dandiker as co-inventors.

7. The Bodor PCT includes the following disclosure of a regimen for treating multiple sclerosis (MS) using cladribine:

> At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant

[1] Serono S.A. is a subsidiary of Patent Owner, Merck Serono S.A. I collectively refer to Ares Trading S.A., its parent Serono S.A., and their other affiliates including Serono International S.A. and Serono Inc., between 2002 and 2004, as “Serono” throughout this declaration.

[2] I understand that IVAX Corporation is an affiliate of IVAX International GmbH. I collectively refer to IVAX Corporation and IVAX International GmbH as “IVAX” throughout this declaration.

> complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered 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.

’480 Ex. 1022, 23:15-20; ’481 Ex. 1022, 23:15-20.

8. The Bodor PCT also includes a disclosure of an “alternative” regimen for treating multiple sclerosis (MS) using cladribine:

> Alternatively the patient would be treated with 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant dosage form once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment.

’480 Ex. 1022, 23:20-24; ’481 Ex. 1022, 23:20-24.

9. The Bodor PCT also includes a reference to two provisional applications apparently filed by IVAX. ’480 Ex. 1022, 23:24-29; ’481 Ex. 1022, 23:24-29. I was not aware of these provisional applications. And I do not know their subject matter.

10. In addition to my recollection and my review of the Bodor PCT, I reviewed the materials cited herein, which refreshed my memory about some details of what occurred from 2002 to 2004.

II. BACKGROUND

11. I was the former Global Head of Quantitative Pharmacology and then Executive Scientific Director in Translational Medicine at Merck Serono and am currently retired. My whole professional career relates to clinical pharmacology and pharmaceutical experience, including 27 years in the pharmaceutical industry. My work at Serono (including at Merck Serono) focused on clinical pharmacology, pharmacodynamics and pharmacokinetics, and translational aspects thereof. My work supported Merck Serono's drug development from concept phase in discovery through late-stage clinical development programs, including regulatory submissions. I have also lectured on bioanalytics, clinical pharmacology, and drug development science, in particular at the School of Pharmacy, Lausanne University, and Lausanne University Hospital, Switzerland. A copy of my current CV is attached as Appendix A.

12. I received my Pharmacists Diploma from Lausanne University in 1980 and a Ph.D. in Pharmacy from Lausanne University in 1985. I completed a 1.5-year postdoctoral fellowship in Pharmacokinetics at UCSF with Professor L.Z.

Benet, were I studied the formation and binding of a tolmetin metabolite (acylglucuronide) in humans.

13. Throughout my career, my work has focused on my core expertise in clinical pharmacokinetics and pharmacodynamics, and I have participated in multiple drug development projects and initiatives. Following my postdoctoral fellowship, I spent 5 years in the Clinical Pharmacology division of Lausanne University Hospital. Then I joined Serono as associate director in Clinical Pharmacology in 1993, while continuing to lecture at the School of Pharmacy at Lausanne University.

14. At Serono, I took successive roles in Serono's Clinical Pharmacology, Pharmacometrics, Human Pharmacology, and Experimental Medicine groups. In those roles, I provided strategic and scientific input to Serono's clinical programs and pre-clinical programs, with special emphasis in study design and data interpretation. I worked as a member of several drug development project teams, including cladribine for treating multiple sclerosis, atacicept for treating rheumatoid arthritis, Iturelix (a growth hormone releasing factor), recombinant proteins for reproductive health (FSH, LH, hCG), Interferon-ß-1a, TNF Binding Protein, and Leukemia Inhibitory Factor.

15. In 2006, Merck acquired Serono and confirmed me in my role. At Merck Serono, I headed the Modelling and Simulation group for 8 years from 2006

to 2014. In 2014, I became Merck Serono's Global Head of Quantitative Pharmacology. In that role, I oversaw Merck Serono's deterministic and stochastic modelers (from Quantitative Systems Pharmacology to Pharmacometry), clinical pharmacokineticists, and clinical pharmacologists to drive and support the discovery, development and commercialization of innovative medicines for patients. I held that role until February 2020, when, in anticipation of my retirement, I took the role of Executive Scientific Director, providing strategic and scientific advice to Merck Serono's Translational Medicine programs. I retired in June 2021.

16. I have co-authored over 70 publications in peer-reviewed journals and presented numerous posters and presentations at international conferences. I have been a member of several professional societies. I was a fellow of the American Association of Pharmaceutical Scientists (AAPS), the Population Approach Group in Europe (PAGE), and the American Society for Clinical Pharmacology and Therapeutics (ASCPT). I have also received patents for my work on cladribine regimens for treating multiple sclerosis and the use of TACI-Ig fusion protein for the manufacture of a medicament for treating lupus erythematosus.

III. DEVELOPMENT OF MAVENCLAD BY SERONO

17. From 2001 through several years after 2004, I was part of a team at Serono that was researching and developing an oral dosing regimen using

cladribine to treat multiple sclerosis ("MS"). My team at Serono started investigating whether cladribine could be used to treat multiple sclerosis in 2001. We pursued cladribine as a potential treatment for MS based on its effects on some biomarkers of MS, but it had not been demonstrated whether cladribine could actually be used safely and effectively to treat MS and, if so, what cladribine dosing regimen might be appropriate. Therefore, in 2003 and 2004, we at Serono were investigating whether a safe and effective oral cladribine regimen could be designed through some combination of particular dosages, lengths of dosing periods, and lengths of cladribine-free periods, in addition to otherwise planning and designing Phase III trials to evaluate whether the dosing regimens were safe and effective.

18. My team at Serono included my co-inventors of the '947 patent and the '903 patent, Drs. Lopez-Bresnahan, Ythier, and De Luca, along with many others.

19. Dr. Ythier, who was my supervisor at the time, and I researched and investigated pharmacokinetics of cladribine to be used in treating patients with MS, with the goal of developing dosing regimens that would be safe and effective. We then used our findings to help design clinical study protocols for Phase III studies of cladribine for treating MS, focusing on what dose and dosing regimen would allow safe, effective treatment.

20. Dr. Lopez-Bresnahan and her team worked with us to design the dosing regimen for the Phase III study protocol(s), designing the inclusion and exclusion criteria, study assessments, and discontinuation criteria (in collaboration with statisticians), and planning all necessary elements to ensure the study was safe and statistically meaningful to demonstrate doses were safe and effective. She then directed and helped manage the Phase III trials.

21. Dr. De Luca was Serono's Chief Intellectual Property Counsel. His discussions with various team members during the development of cladribine for treating MS contributed to our development of a proposed dosing regimen.

22. The work of our team at Serono ultimately led to the development of the drug Mavenclad® and its unique dosing regimen, which is approved by the FDA, and the authorities in many other countries, to treat MS. Our work also led to patents, including the '947 patent and the '903 patent, which claim dosing regimens for treating MS.

IV. COLLABORATION WITH IVAX

23. In October, 2002, Serono partnered with IVAX to develop an oral formulation of cladribine. Ex. 2048.[3] I refer to this agreement between Serono

[3] All citations to Patent Owner's Exhibits are in reference to Patent Owner's exhibits filed contemporaneously in IPR2023-00480 and IPR2023-00481.

and IVAX, which is titled "Product Development and License Agreement," as the "Joint Research Agreement." *Id*. The Joint Research Agreement defined the respective roles of Serono and IVAX as follows.

24. IVAX agreed to "develop an oral dosage formulation of [cladribine] in tablet or capsule form suitable for use in clinical trials and commercial sale." *Id.*, 19-20 (emphasis added). IVAX also agreed to conduct Phase I trials of its cladribine formulation, which the Joint Research Agreement described as "a pharmacokinetic study," and to furnish Serono with its results and "all data, information and documentation reasonably required to enable [Serono] to carry out the clinical trials necessary for health authority approvals." *Id.*, 20-21.

25. Serono agreed to "conduct clinical trials," to determine "the dose, safety, and/or efficacy" of cladribine's oral tablets or capsules. *Id.*, 2, 17-18. Serono also agreed to "assume all responsibilities and costs associated with statistics and data management, regulatory affairs, clinical quality assurance, safety studies toxicology and the clinical development of the [final product]." *Id.*, 20-21. Further, Serono agreed to "obtain necessary health authority approvals, and market the final product in the United States and all [major European countries]." *Id.*, 17-18, 22.

26. After signing the Joint Research Agreement, IVAX and Serono each performed their respective roles in developing cladribine for treating MS, as

agreed. *E.g.*, Ex. 2050; Ex. 2049. IVAX developed an oral dosage formulation of cladribine—solid tablets containing what they called a "complex cladribine-cyclodextrin complex"—and performed Phase I pharmacokinetic ("PK") studies using a single dose of their formulation. *E.g.*, '480 Ex. 1022, 33:24-25; '481 Ex. 1022, 33:24-25 ("This study was a 2 center, open-label, randomized, 4-way crossover single dose study using twelve patients with MS."). Drs. Bodor and Dandiker were both part of the IVAX team who collaborated with my team at Serono. Using IVAX's oral dosage formulation, my team at Serono developed a dosing regimen for treating MS and performed several Phase I trials, as well as Phase III clinical trials using this regimen, that ultimately led to regulatory approval of MAVENCLAD® (tablets comprising IVAX's formulation dosed according to our regimen) for treating MS.

27. Confidential communication between the Serono team and the IVAX team took place both at meetings (both in person and by telephone), where formal presentations were made, and by e-mail.

28. The IVAX and Serono teams met or corresponded regularly to discuss project progress and various issues. For example, the teams from Serono and IVAX met in Amsterdam on August 27, 2003 to discuss the development of cladribine for treating MS. Ex. 2050. The minutes of that meeting show that Dr. Steve Marcus and Dr. Yogesh Dandiker of IVAX attended the meeting. Dr.

Marcus presented on "Phase I studies" for the "cyclodextrin formulation" of cladribine. *Id.*, 2-3. Dr. Dandiker, a co-inventor of the Bodor PCT, and D. Emma (also of IVAX) presented on "Formulation progress" for soft gel, hard gel, and tablet formulations of cladribine. *Id.*, 3-4. Dr. Lopez-Bresnahan from my team at Serono, one of the co-inventors of the '947 patent and the '903 patent, presented on "Phase III [study] design," including doses and regimens for treating MS with cladribine. *Id.*, 4-5. I was present at that meeting and confirm that the minutes accurately reflect the work Drs. Marcus, Dandiker, Emma, and Lopez-Bresnahan discussed.

29. As another example, on December 17, 2003, Isabelle Emery of Serono emailed a draft Regulatory Briefing Document to the team at Serono, including me, and the team at IVAX, including Dr. Dandiker, the co-inventor of the Bodor PCT, and Dr. Marcus. Ex. 2049, 1. The Regulatory Briefing Document, which I contributed to, contained a "Proposed Phase 3 Study" designed and developed by Serono inventors. *Id.*, 47-51. This email asked various members of the Serono and IVAX teams to review portions of the Briefing Document. *Id.*, 1-3. In particular, Dr. Dandiker of IVAX, a co-inventor of the Bodor PCT, was asked to review the section on "Chemistry, Manufacturing, and Controls," which addressed the formulation of cladribine, how it was to be manufactured, and the quality control processes to be used. *Id.* I was asked to review the section on

"Pharmacokinetics and Pharmacodynamics." *Id.* And Dr. Lopez-Bresnahan from my team at Serono was asked to review the entire document, including the section on the "Clinical Development Plan," which included the dosage and regimens to be administered to patients. *Id.* This distribution of tasks reflected the distribution of responsibilities as per the Joint Research Agreement.

V. COMMUNICATIONS BETWEEN SERONO AND IVAX

30. In the Joint Research Agreement, Serono and IVAX agreed to confidentially share information and communicate frequently about the ongoing development of cladribine for treating MS. Ex. 2048, 18, 22. IVAX agreed to furnish Serono with the results of its Phase I pharmacokinetic trials of an oral dosage formulation of cladribine and "all data, information and documentation reasonably required to enable [Serono] to carry out the clinical trials necessary for health authority approvals." *Id.*, 20-21. Serono agreed to "keep [IVAX] generally informed as to [Serono's] progress in these efforts" (that is, in determining dosage regimens, planning, designing, and conducting Phase III trials, obtaining regulatory approval, and marketing and selling the final product). *Id.*, 22. The parties mutually agreed that information they shared would be kept confidential and would "not be disclosed to third parties and [would] be made available only to recipient's employees or independent contractors who agree in writing to equivalent

conditions and who have a need to know the information for the purposes specified under [the agreement]." *Id*., 30.

31. To facilitate this communication, the Joint Research Agreement established a "Joint Development Committee…comprising at least two representatives from each" of Serono and IVAX. *Id.*, 18. This Joint Development Committee was required to meet "as often as necessary," and at least "within sixty (60) days…" *Id.* This Joint Development Committee did meet regularly through 2003 and 2004. *E.g.*, Ex. 2050. For example, as I will describe in more detail below, our teams met in Amsterdam on August 27, 2003 to discuss our respective progress of Phase I trials, formulation work, and planning for Phase III trials. Ex. 2050. I was present at that meeting in Amsterdam, which also included Dr. Dandiker of IVAX, co-inventor of the Bodor PCT, and several other members of the IVAX team, including Dr. Marcus. *Id.*

32. In addition to formal meetings of the Joint Development Committee, my team at Serono and the team at IVAX exchanged numerous emails and documents. These emails included, for example, informal discussions and drafts of regulatory documents. Recipients included Dr. Dandiker of IVAX, co-inventor of the Bodor PCT, Dr. Marcus, and several other members of the IVAX team. For example, as I discuss in more detail both above and below, on December 17, 2003, Isabelle Emery of Serono emailed a draft Regulatory Briefing Document to my

team at Serono and the IVAX team to ask members of both teams to review the draft. Ex. 2049.

VI. SERONO TEAM'S DEVELOPMENT OF THE REGIMEN DISCLOSED IN THE BODOR PCT

33. Ultimately, I and my team at Serono, and not anyone at IVAX, were the first and only people to design and develop the regimen for treating MS which is disclosed in the Bodor PCT. The IVAX team did not contribute to the design or development of that dosing regimen or the unique weight-based regimen that we later claimed in the '947 patent and the '903 patent.

34. In particular, Dr. Lopez-Bresnahan and I, with the support of Drs. Ythier and De Luca, designed a regimen for treating MS by administering oral cladribine 10 mg tablets daily for 5-7 days per month for 2 months followed by a 10-month cladribine free period. This occurred before February 2004 (when, I am informed by counsel, the first provisional application containing this disclosure, U.S. Application No. 60/541,247, was filed by IVAX, naming only Dr. Bodor as an inventor). Our development of the regimen in 2003 is documented, for example, in the minutes of the August 2003 Amsterdam meeting, Ex. 2050, as well as in the December 2003 Regulatory Briefing Document, Ex. 2049.

A. August 2003 Presentation

35. By August 2003, I and my team at Serono had designed dosing regimens where cladribine was administered orally for periods of five consecutive

days in a month, repeated each month until the target effective dose was reached. Ex. 2050, 4-5. One particular regimen we had developed involved two months of treatment: five consecutive days in the first month, then five consecutive days in the second month.

36. My colleague Dr. Lopez-Bresnahan presented one such regimen at a meeting in August 2003, which I described above. *Id.* The minutes of that meeting show that Dr. Lopez-Bresnahan presented a "Phase III [study] design," including two regimens for treating MS with oral cladribine. *Id.* The minutes identify the two regimens as "treatment arms" for the proposed study: one with a "cumulative dose approximating 0.7 mg/kg" and one with a cumulative dose approximating "2.1 mg/kg." *Id*., 4. Certain other Serono documents refer to the "0.7 mg/kg" dose as the "low" dose and to the "2.1 mg/kg" dose as the "high" dose. *E.g.*, Ex. 2049, 48.

37. The minutes also state that in both arms the doses would be delivered as "5 days" per month for a number of months. Ex. 2050, 4-5. The low dose arm would be delivered by a regimen of:

"5 *days* × 2 *months.*"

Id.[4] She also stated that each dose would be delivered using one of IVAX's oral formulations, the development of which had been discussed earlier at that meeting.

38. As Dr. Lopez-Bresnahan described at the August 2003 meeting, the two months of treatment (or, for the high dose arm, six months of treatment) were followed by the remainder of the "[d]uration of treatment" which was "24 months." *Id*. For patients in the low dose arm, who would receive cladribine during 5-days in each of 2 months, the period without treatment would have been a "cladribine-free period" of 22-months. For patients in the high dose arm, who would receive six months of cladribine, the period without treatment would have been a "cladribine-free period" of 18-months.

B. December 2003 Briefing Document

39. By December 2003, I and my team at Serono had refined the dosing regimens for the planned Phase III trial to use 10 mg solid tablets and have a retreatment period 12 months after the first treatment period. Ex. 2049. Thus, in

[4] The minutes of the August 2003 Meeting describe this regimen as a "cumulative dose approximating 0.7 mg/kg ([0].35 mg/kg × 5 days × 2 months)." Ex. 2050, 4. 0.35 mg/kg is half the approximate cumulative dose, so this means 0.35 mg/kg per month for 2 months, delivered over 5 consecutive days each month.

the regimen my team at Serono had developed by December 2003, a two-month initial treatment period would be followed by a ten-month cladribine-free period.

40. For example, on December 17, 2003, Isabelle Emery of Serono circulated via email a draft Briefing Document to my team at Serono and to the IVAX team, including Dr. Dandiker and Dr. Marcus, which I described above. *Id.* This document included a description of our plan for Phase III trials of cladribine for treating MS, which was developed by the Serono team, including Drs. Ythier, Lopez-Bresnahan, De Luca, and me. *Id.*, 47-51.

41. Similar to Dr. Lopez-Bresnahan's August 2003 presentation, the study treatment plan in the December 2003 Briefing Document included three arms, which would receive a cumulative dose of 2.1 mg/kg, a cumulative dose of 0.7 mg/kg, or just placebo. *Id.*, 47. This Briefing Document refers to these as the "high," "low," and "placebo" doses. *Id.* It further discloses that patients in the high or low dose arm will receive 10 mg solid tablets for "5-day consecutive dosing" each month for a predetermined number of months, as discussed in more detail below. *Id.*, 13-18, 49.

42. The December 2003 Briefing Document also described the design of the study in more detail, including the proposed dosing regimen and the "double-blind" protocol. *Id.*, 47-49. Double-blind study design, which avoids bias by concealing from both the patients and the treating physicians which arm each

patient is in, is an important aspect of clinical studies like this proposed Phase III trial. The longest active treatment duration in the study would be the high dose arm. The December 2003 Briefing Document teaches that the high dose arm would receive six months of active treatment:

"5-*day*[*s*] [/ *month*] × 6 [*months*]" = 2.1 *mg*/*kg*

Id., 49. This is the treatment schedule we described in the minutes of the August 2003 presentation, which describes the same high dose arm as:

5 *days* × 6 *months*

Ex. 2050, 4. As a result, a double-blind study design required 6 months of "treatment" for every patient.

43. The planned high and low doses would have been delivered as either a 10 mg cladribine tablet or a placebo, as appropriate, to obtain the correct total dose. Specifically, in the "Assignment to treatment groups" section of "Table 5.1-1: Synopsis of the Proposed Phase 3 Study," under "Blinding," it states that "all patients receive [the] same number of tabs (i.e., low dose patients receive placebo to fill out high dose cycles, any decrease in active treatment dose is replaced with placebo…)." Ex. 2049, 49. This Briefing Document summarizes the regimen as "6 cycles (high/low/placebo)" followed by 6 months of no treatment and then "6 cycles (low/low/placebo)" after 12 months. *Id*., 47-48.

44. Thus, I and my team at Serono communicated that patients in the "low" dose treatment arm (0.7 mg/kg) would receive two months of cladribine followed by 4 months of placebo. 0.7 mg/kg is exactly one-third of the 2.1 mg/kg "high" dose. Thus, at the same rate of treatment, a patient in the low dose arm would receive a 0.7 mg/kg dose in exactly one-third of the time:

$$0.7\ mg/kg = 2.1\ kg/mg\ /\ 3$$
$$= (5\ days/month \times 6\ months)\ /\ 3$$
$$= 5\ days/month \times 2\ months$$

This is the treatment schedule we described in the minutes of the August 2003 presentation, which describes the same low dose arm as:

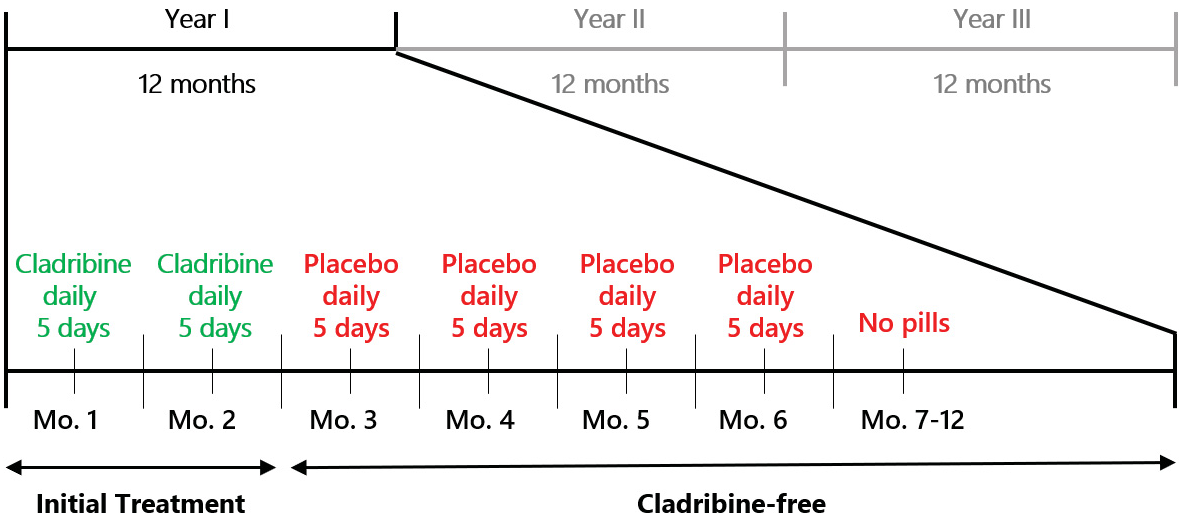
$$5\ days \times 2\ months$$

Ex. 2050, 4.

45. The December 2003 Briefing Document explained patients would receive additional treatment 12 months after the first treatment began. Ex. 2049, 47-51. Although the Briefing Document describes this as "6 cycles" of "repeat treatment … at 12-18 months …" *Id*., 48, 49 (patients "will receive blinded re-treatment at 12-18 months"), it is clear from the context of the document that this meant repeat treatment 12 months *after* the initial treatment, during months 13-18. For example, if retreatment were to occur during each of months 12-18, that would result in 7 cycles of retreatment, not the described "6 cycles." Further, the Briefing

Document discloses that 3 phases, each with 6 cycles of treatment, added up to a "36 month" duration. *Id*., 47-49. This shows that each phase would take 12 months—6 months of treatment and/or placebo (depending on which arm a patient was in) followed by 6 months with no treatment—so the treatment in the second phase would begin in month 13.

46. Therefore, patients in the "low" dose treatment arm would receive treatment in months 1 and 2, placebos in months 3-6, and 6 months with no pills. *Id*., 49. This would result in a 10-month "cladribine-free" period. This is illustrated in the following figure, which I prepared:



47. In December 2003, we at Serono were also considering administering cladribine to patients for 6 or 7 days per month, including in the low dose arm. The December 2003 Briefing Document and the "Study Treatment" section were in a draft stage. The Serono inventors discussed (e.g., during joint meetings that

IVAX attended) that certain parameters in the study protocol, such as the number of days of cladribine dosing each month, might need minor adjustment, e.g., to 6 or 7 days per month.

48. I and my team at Serono envisioned additional details of the proposed Phase III trials, including additional details about the proposed dosing regimen, that are not reflected in the Bodor PCT or the ’247 provisional. While the December 2003 Briefing Document includes the dosing regimens disclosed in the Bodor PCT and the ’247 provisional, the Bodor PCT and the ’247 provisional do not include all the details in our December 2003 Briefing Document. Thus, the Bodor PCT does not disclose the full scope of what my team at Serono envisioned or communicated in 2003.

49. After December 2003, I and my team at Serono continued our development of regimens to treat MS using cladribine. Serono ultimately prepared and submitted requests for regulatory approval of cladribine for treating MS. My team at Serono, and not the team at IVAX, planned and conducted Phase III trials that studied different dosing regimens of cladribine for treating MS. IVAX provided its oral formulation but did not otherwise contribute to the design of the dosing regimen. And my team at Serono, and not the team at IVAX, got regulatory approval to market the resulting drug—Mavenclad®.

VII. THE SERONO TEAM COMMUNICATED ITS REGIMEN TO THE IVAX TEAM

50. After I and my team at Serono designed both of the regimens disclosed in the Bodor PCT—the 2-month regimen which I understand Petitioner cites and the 6-month "alternative" regimen—we confidentially communicated them to the joint project team, including IVAX, for example at the August 2003 meeting and in the December 2003 Regulatory Briefing Document, discussed above, well before February 2004. The team at IVAX who received our communications included at least Dr. Dandiker, one of the named inventors of the Bodor PCT, and Dr. Marcus.

51. For example, the August 27, 2003 presentation that I discussed above was presented by my colleague Dr. Lopez-Bresnahan to members of the IVAX team, including to Dr. Dandiker and Dr. Marcus, and communicated the then-proposed dosing regimen of daily oral cladribine tablets for 5 days per month for 2-months followed by a 22-month cladribine-free period developed by my team at Serono. Ex. 2050, 4-5. It also communicated to the IVAX team my team at Serono's alternative dosing regimen of daily oral cladribine tablets for 5 days per month for 6-months followed by an 18-month cladribine-free period, which I understand is also disclosed in the Bodor PCT. *Id*.; '480 Ex. 1022, 23:20-24; '481 Ex. 1022, 23:20-24.

52. Further, the Briefing Document that I discussed above was e-mailed by Isabelle Emery of Serono to members of the IVAX team, including to Dr. Dandiker and Dr. Marcus, on December 17, 2003, and communicated to IVAX the proposed dosing regimen using daily 10 mg oral cladribine tablets for 5 days per month for two months followed by a 10-month cladribine-free period that I and my team at Serono had designed. Ex. 2049, 47-51; *above* ¶¶44-45.

53. Communications from my team at Serono, including but not limited to these two documented communications, conveyed to IVAX, including at least Dr. Dandiker, my team at Serono's proposed dosing regimen using daily 10 mg oral cladribine tablets for 5-7 consecutive days per month for two months followed by a 10-month cladribine-free period. The communications also included our alternative proposed dosing regimen using daily 10 mg oral cladribine tablets for 5 consecutive days per month for six months followed by an 18-month cladribine-free period. These regimens, which my team at Serono communicated to IVAX, appear to be the basis for the regimens that are disclosed in the Bodor PCT.

54. To the best of my knowledge, IVAX did not design or develop any regimen for treating MS using cladribine, let alone the regimen of administering 10 mg of oral cladribine tablets per day for 5-7 days per month for 2 months followed by a 10-month cladribine free period that I and my team at Serono designed and communicated to IVAX before February 2004. Developing a dosing regimen for

treating MS was the role my team at Serono agreed to perform, and not a role the team at IVAX agreed to perform or actually performed. To the best of my knowledge, no one on the IVAX team ever mentioned any work they did or ideas they had related to regimen development. The IVAX team provided tablets and initial Phase I study data at IVAX's expense to support my team at Serono's development of a dosing regimen for cladribine. When my team at Serono communicated its regimen to the team at IVAX, no one on the IVAX team suggested that anyone on the IVAX team had developed a similar dosing regimen—or any dosing regimen.

55. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

56. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and 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 Section 1001 of Title 18 of the United States Code.

Dated: December 21, 2023 By: _____

Alain Munafo, Ph.D.

APPENDIX A

CURRICULUM VITAE

ALAIN MUNAFO

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PERSONAL DATA

Date of birth:	May 29, 1956 in		Lausanne, Switzerland
Origin:	Mauraz (VD), Switzerland	Marital status:	Divorced, one child

Languages: French (mother tongue), fluent English and basics in German

CAREER OBJECTIVES

To provide scientific leadership in drug development, making use of my clinical pharmacology expertise associated with strategic Modeling & Simulation experience, in a dynamic organisation with international exposure.

CAREER SUMMARY

A confirmed professional PhD - pharmacist - and clinical pharmacologist, specialized in early clinical development, with more then 20 years of biopharmaceutical industry experience, 5 years of Clinical Pharmacology in a University Hospital, and another 7 years postgraduate academic training. Deployment, development and management of various Merck Serono groups, currently of managerial responsibility of Quantitative Pharmacology Department. A large experience in designing, directing, analyzing and reporting early clinical studies in human, with a special emphasis on proof of biological activity, pharmacokinetics and pharmacodynamics, modeling and population approaches, up to worldwide regulatory submissions. Sustained practice in Project management, with leadership and participation in several product development programs. Up-to-date knowledge, and extensive use of computers. University teaching experience. Author and co-author of more than 100 scientific papers and abstracts.

PROFESSIONAL EXPERIENCE

1993 to present **Ares-Serono,** then **Serono International S.A.** and now **Merck Serono S.A.**, Geneva/Aubonne/Lausanne, Switzerland, an affiliate of **Merck KGaA**, Darmstadt, Gernany

A global integrated biopharmaceutical company, leader in Immuno-oncology, Oncology and in the treatment of auto-immune and neurological disorders, in particular Multiple Sclerosis, and involved as well in infertility, growth and metabolism.

February 2020 to now **Executive Scientific Director, Translational Medicine**

Actively supports the success of the Merck Biopharma R&D organization by providing advice and expertise to Translational Medicine with research and development strategic leadership at all stages of the value chain. This role provides advice and consult from concept phase in discovery through late-stage clinical development programs, delivering the respective data for submission, and supporting Life Cycle Management. .

2013 to now **Site Head** for the Merck-Serono facility in the EPFL

2014-2020 **Global Head of Quantitative Pharmacology**

Senior Director then **Executive Director** (2016)

Managerial, strategic and scientific role, leading the Department (up to 50+ collaborators: Clinical Pharmacology, Pharmacometry and Translational Quantitative Pharmacology) to drive and support the discovery, development and commercialization of innovative medicines for patients.

2006-2014 **Senior Scientific Director, Head of Modeling & Simulation**

Development and direction of the Modeling & Simulation group within the Clinical Development Organisation and interfacing with Preclinical Department and external parties, for all drugs in the development portfolio.

2003-2006 **Clinical Science Director, Experimental Medicine/Clinical Research**

Development and direction of Proof of Concept studies[*]*, and scientific input into Clinical Teams and Global Product Development; responsibility in selected preclinical project teams with respect to the transition into Clinical Development; due diligence review of new opportunities.*

2000-2003 **Senior scientific advisor, Human Pharmacology Group**

Strategic input to the department operations and clinical program, with special emphasis in study design and data interpretation; global responsibility in special projects; inter- and intra-departmental training and coaching activities. Full-member of several drug development project teams, including collaboration with third parties.[†]

1996-2000 **Corporate director, Pharmacometrics**

with global responsibility in human pharmacokinetics and pharmacodynamics of peptides[‡] *and recombinant proteins*[§]*, from the human pharmacology development plan and phase I program up to submission/registration.*

Member of several project teams, as well as project leader for a compound[**] *with potential in embryo implantation.*

1993-1995 **Corporate clinical pharmacology associate director**

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[*] *e.g. atacicept in Rheumatoid Arthritis*

[†] *e.g. Cladribine by oral route*

[‡] *e.g. Growth Hormone Releasing Factor (Iturelix), in its native or pegylated form*

[§] *e.g. Reproductive health (FSH, LH, hCG), Growth Hormone, Interferon-ß-1a, TNF Binding Protein*

[**] *Leukemia Inhibitory Factor*

1990-2000	**School of Pharmacy,** Lausanne University, Switzerland
1992-2000	**Privat-Docent** *teaching bioanalytics.*
1990-1992	**Associate professor** *ad interim*
1987-1992	**Clinical Pharmacology Division**, Lausanne, CHUV, Switzerland
1991-1992	**Research project manager**, chief of the laboratory
1987-1991	**Research associate**
	Responsible for the clinical pharmacology laboratory and for data analysis of phase I studies; cooperated in the Therapeutic Drug Monitoring and Consultation service in close connection with clinicians.

POSTGRADUATE TRAINING

1986-2017	Numerous courses, symposia and workshops on technical, managerial and functional matters.
1990	Diploma **Clinical Pharmacologist** "SPTC"
1986-1987	**Visiting research postdoctoral fellowship** Department of Pharmacy, School of Pharmacy University of California, San Francisco (UCSF), USA
1980-1985	Postgraduate fellowship Institut of Pharmaceutical Analysis School of Pharmacy, Lausanne University **Ph.D. thesis** (Doctorat en Pharmacie) "*cum laude*", November 1985

EDUCATION

1974-1980	Pharmacy Studies School of Pharmacy, Lausanne University **Swiss federal diploma of Pharmacist**, May 1980
1966-1974	Pregraduate schools in Lausanne, Montreux and Vevey Mathematics and Science section ***Maturité*, type C** (Sciences), July 1974

PUBLICATIONS AND PRESENTATIONS LIST

Available upon request

PATENTS – (CO-)INVENTOR

Cladribine regimen for treating multiple sclerosis, EPC 2010
Dosing methods for treating autoimmune diseases using TACI-Ig fusion protein such as atacicept, EPC 2010

SCIENTIFIC SOCIETIES AFFILIATIONS

American Association of Pharmaceutical Scientists (AAPS)
Population Approach Group in Europe (PAGE)
American Society for Clinical Pharmacology and Therapeutics (ASCPT)

HOBBIES

Sport (sailing, skiing), photography, reading and travelling.

Lausanne, 11.06.2020