UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MARINUS PHARMACEUTICALS, INC.,
Petitioner

v.

OVID THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00020
Patent 11,395,817

SUPPLEMENTAL DECLARATION OF SHARON BAUGHMAN, Ph.D.

MARINUS 1060
Marinus v. Ovid
PGR2023-00020

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REFERENCES CITED

Exhibit	Description
1001	U.S. Patent No. 11,395,817 to Ovid Therapeutics, Inc. "the '817" or "the '817 patent"
1055	Supplemental Information to Vaitkevicius et al., "Intravenous Ganaxolone for the Treatment of Refractory Status Epilepticus: Results from an Open-Label, Dose-Finding Phase 2 Trial," *Epilepsia* 63:2381-91 (2022) ("*Epilepsia* Supplemental Information" or "*Epielpsia* SI")
2003	H. Vaitkevicius et al., Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial, 63 *Epilepsia* 2381-2391 (2022)
1061	Gasior et al., Intravenous ganaxolone: Pharmacokinetics, pharmacodynamics, safety, and tolerability in healthy adults, *Clin. Pharmacology in Drug Dev.* (2024)

I, Sharon Baughman, declare as follows:

I. INTRODUCTION

1. I am being offered as an expert on behalf of Petitioner Marinus Pharmaceuticals, Inc. ("Marinus") to provide opinions and testimony in response to Ovid's Patent Owner Response related to Marinus's Petition for Post-Grant Review of U.S. Patent No. 11,395,817 (Ex. 1001).

II. BACKGROUND AND MATERIALS CONSIDERED

2. This declaration and opinions set forth herein are based on the references and other documents listed above ("References Cited"), and my personal education, professional experience, and general knowledge of the art as of the 2016 timeframe.

3. This declaration sets forth the bases and reasons for my opinions from the perspective of a person with over 20 years of experience in the biotechnology industry in the areas of preclinical and clinical pharmacokinetics,

pharmacodynamics, bioanalysis and adsorption, distribution, metabolism, and excretion (ADME) of protein and small molecule entities.

4. This declaration is based on information currently available to me. I reserve the right to continue my investigation and study, which may include a review of documents and information that Ovid presents in response to this declaration.

III. EDUCATION, PROFESSIONAL EXPERIENCE, AND QUALIFICATIONS

5. I have attached my curriculum vitae as **Exhibit A** to this declaration. I have summarized my educational and professional background below.

6. I completed my B.S. in Chemistry at the University of New Orleans and later completed my Ph.D. in Physical Organic Chemistry at Rice University.

7. I have extensive experience in the pharmacokinetics of biologics. I worked at Genentech from 1990 to 1999 and at Amgen from 1999 to 2009. As a result, I have a strong working knowledge of what is needed for the development of a successful drug, including dose, frequency of dosing, route of administration, patient considerations, cost of goods, regulatory demands, and most importantly, safety and efficacy.

8. At Genentech, I was Associate Director of Pharmacokinetics and Drug Metabolism. I was directly responsible for or managed professionals who were responsible for the nonclinical and clinical research and development of multiple

drug products, including: growth hormone, TPA, DNase, IGF-1, Lenercept, Herceptin® (trastuzumab), Rituxan® (rituximab), Avastin® (bevacizumab), and other research projects. I was also a project team leader and preclinical pharmacology team lead. My responsibilities included the design, conduct, analysis, and reporting of nonclinical and clinical studies to support regulatory filings for approval of the drug. As such, pharmacokinetic and pharmacodynamics modeling, writing of regulatory documents, attending FDA and other regulatory meetings, and dose selection were critical aspects of my job.

9. At Amgen, I was the Director of Pharmacokinetics and Drug Metabolism,. I was responsible for the PK/PD and assay groups. At one point, 125 professionals reported to me. At Amgen, our group was responsible for the PK/PD, population PK and clinical pharmacology of EPO, Neupogen® (filgrastim), Neulasta® (pegfilgrastim), Anakinra, denosumab, Enbrel® (etanercept), and multiple other entities. I was also responsible for the analytical laboratory, which developed, validated, and ran the assays for measurement of the biologic in various matrices. My responsibilities in this role were similar to those that I had while at Genentech, noted above.

10. In 2009, I left Amgen and became an independent consultant in the areas of pharmacokinetics, pharmacodynamics, and assays for biologics and small

molecules. The company I founded, ProPharma Services, has expanded to include several additional professionals with backgrounds in biologics and small molecule pharmacokinetics, pharmacodynamics, drug metabolism, and drug research and development. We have multiple clients, mainly small start-ups, although we have also been contracted by companies such as Merck (lecturer in the PK and drug development of protein therapeutics, 2009) and Roche (for expert opinion and to teach courses on the PK/PD/assays of biologics).

11. In addition, in 2009, I was a faculty member at the University of Wisconsin teaching a course on "Drug Development for Biologics and Small Molecules." Our group supports both nonclinical and clinical drug development, and we have also been involved in many meetings with regulatory bodies, including in the United States, EU, and Australia.

12. In the early 1990s, I was responsible for the nonclinical and clinical PK development of Herceptin® (trastuzumab), one of the first humanized monoclonal antibodies approved by FDA, and a drug eventually used in the treatment of breast cancer. The work began with the murine monoclonal antibody against HER2/neuprotein (Receptor tyrosine-protein kinase erbB-2). Due to high immunogenicity observed in the preclinical studies, the murine monoclonal antibody was humanized. This biologic underwent preclinical toxicology/toxicokinetic

studies by both the intravenous (IV) and subcutaneous (SC) routes. Once safety studies (monkey) demonstrated the tolerability of the biologic, and pharmacology studies (mice xenografts) demonstrated efficacy in an animal model of disease, the biologic then proceeded to clinical development. For clinical development, the IV infusion route was chosen due mainly to reimbursement issues at the time (SC was not reimbursed), as well as potential concerns as to monitoring the rate of delivery of large amounts of the novel biologic. I was the PK scientist responsible for the Phase 1, 2, and 3 PK of Herceptin® (trastuzumab), and I played a major role in selecting the dose for Phase 3. I was also one of the several individuals responsible for interacting with the patient advocates, and ultimately helped bring them into the discussions of clinical protocol design. This was extremely important, as the patient advocates were well-read and had insight into treatments, treatment effects, and patient issues.

13. I was also involved in the development of Rituxan® (rituximab), a chimeric IgG1 antibody initially investigated and approved for treatment of non-Hodgkin's lymphoma, at the clinical stage, including the writing of the Biologics License Application (BLA) and studies to determine bioequivalence of IDEC Pharmaceuticals and Amgen products. Both the Herceptin® (trastuzumab)

(approval 1998) and Rituxan® (rituximab) (approval 1997) experiences gave me strong insight into pharmacokinetic issues involved in drug development.

IV. ANALYSIS AND OPINIONS

14. I received and reviewed pharmacokinetic information related to ganaxolone that Marinus submitted to FDA.

15. Marinus modeled IV ganaxolone (GNX) dosing scenarios with a 3-compartment model that was developed based on the results of Study 1042-0405, in which IV doses of GNX were given in a variety of bolus and infusion regimens. According to the information from Marinus, this model was originally developed in Berkeley-Madonna software, and subsequently adapted into a series of equations in Microsoft Excel. The model parameters are shown below. Doses are introduced into the central compartment according to the targeted dosing regimen. Concentrations in plasma are predicted as the mass of GNX in the central compartment / Vc.

Term	**Symbol**	**Value**	**Unit**
Volume of the central compartment	Vc	33.3	L
Elimination from the central compartment	kel	1.86	h^{-1}
Distribution from the central compartment to a shallow compartment	K12	1.3	h^{-1}

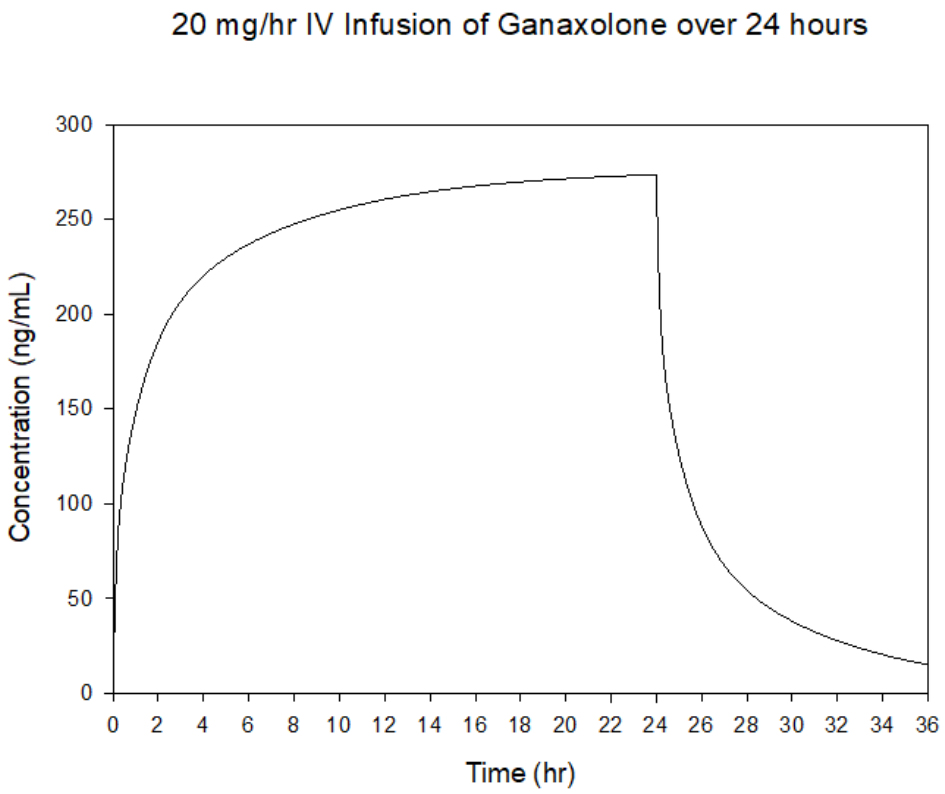
Distribution from the a shallow compartment to the central compartment	K21	0.65	h^{-1}
Distribution from the central compartment to a deep compartment	k13	0.91	h^{-1}
Distribution from the a deep compartment to the central compartment	k31	0.084	h^{-1}

16. After reviewing the information above, as well as the information in the Gasior 2024 paper (Ex. 1061), I ran modeling with WinNonlin, a well-known modeling software in the field of pharmacokinetics, using a three-compartment model to simulate potential dosing scenarios for IV administration of ganaxolone.

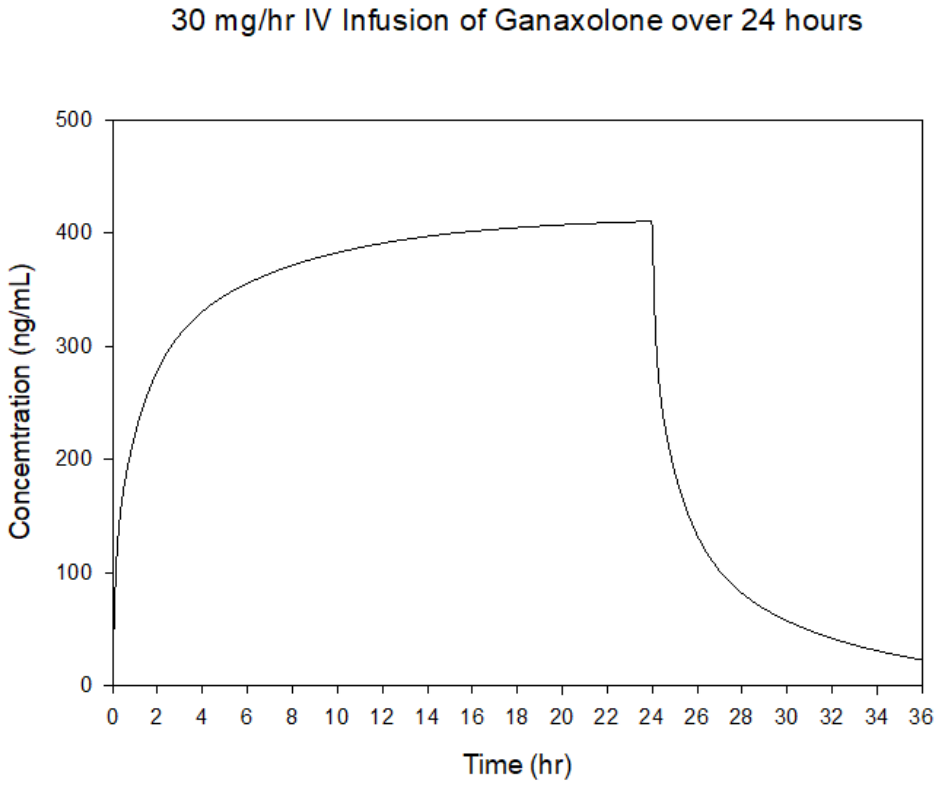
17. In particular, I used the WinNonlin modeling to simulate two potential dosing scenarios: (1) 20 mg/hr of ganaxolone given as a continuous IV infusion over 24 hours (i.e., 480 mg total over 24 hours), and (2) 30 mg/hr of ganaxolone given as

a continuous IV infusion over 24 hours (i.e., 720 mg total over 24 hours). Neither of these simulated scenarios include a bolus dose of ganaxolone.

18. The modeled results for the 20 mg continuous infusion simulation are shown below (linear, semi-log):



19. The modeled results for the 30 mg continuous infusion simulation are shown below (linear, semi-log):

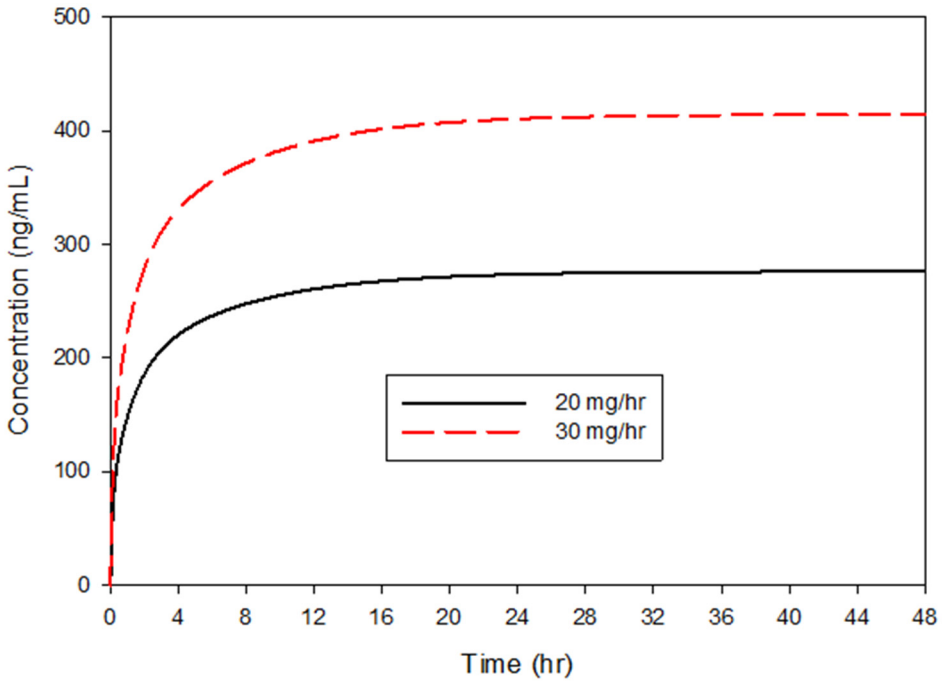


20. The table below shows the pharmacokinetic parameters predicted by the two simulated dosing scenarios:

Dose Group	Cmax (ng/mL)	24-hour AUC (hr*ng/mL)
20 mg/hr	273	5868
30 mg/hr	410	8801

21. In particular, the 20 mg/hr simulation predicts a Cmax of 273 ng/mL within the 24-hour period. The 30 mg/hr simulation predicts a Cmax of 410 ng/mL within the 24-hour period.

22. In order to confirm that steady-state plasma concentration was reached, I also included a 48-hour dosing simulation, shown below.



23. I compared my results with the modeled pharmacokinetic curves that appear as Figure 2 in the Vaitkevicious paper on Marinus's Phase II clinical trials (Ex. 2003 at 2384)). The particular dosing regimens that underlie those models are shown in Supplemental Table 1 (Ex. 1055). The modeled scenarios in Figure 2 all

used an initial bolus dose of ganaxolone and varied the infusion rates during the treatment.

24. To verify the accuracy of my modeling, I compared the output of my model with the modeled data in Figure 2 of Ex. 2003.

I declare under the penalty of perjury that the foregoing is true and correct.

Executed on March 22, 2024.

Sharon Baughman, Ph.D.