

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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OVID THERAPEUTICS INC.,  
Petitioner,

v.

MARINUS PHARMACEUTICALS, INC.,  
Patent Owner.

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IPR2024-00726  
Patent 11,110,100 B2

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Before ERICA A. FRANKLIN, ULRIKE W. JENKS, and  
SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

DECISION  
Denying Institution of *Inter Partes* Review  
35 U.S.C. § 314

## I. INTRODUCTION

Ovid Therapeutics, Inc. (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1–21 of U.S. Patent No. 11,110,100 B2 (Ex. 1001, “the ’100 patent”). Paper 1 (“Pet.”). Marinus Pharmaceuticals, Inc. (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”).

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314. Upon considering the parties’ arguments and evidence, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition. Accordingly, we do not institute an *inter partes* review of the challenged claims.

### A. *Real Parties-in-Interest*

Petitioner identifies itself as the real party-in-interest. Pet. 62. Patent Owner identifies itself as the real party-in-interest. Paper 3, 1.

### B. *Related Matters*

The parties relay that there are no related matters. Pet. 62; Paper 3, 1.

### C. *The ’100 Patent*

The ’100 patent relates to methods of treating status epilepticus (SE), “a life-threatening neurological emergency associates with significant morbidity and mortality,” with ganaxolone (GNX). Ex. 1001, 1:13–15, 2:61, 45:27. According to the Specification:

SE presents as a prolong[ed] seizure for a period of at least 5 minutes or without recovery between seizures. Suppression of SE typically breaks the seizures (i.e., suppresses or reduces the seizure activity). Clinically, suppression of SE can be [a] reduction in seizure burden (i.e., the percent of time during which there is electrographic seizure activity).

*Id.* at 27:57–67. “Seizures are detected in the brain by measuring electroencephalography (EEG) activity” as “[t]here can be seizures (in the brain) that will not be manifested as convulsions and can only be detected by EEG activity.” *Id.* at 46:29–30. The Specification refers to “seizure activity” as encompassing convulsions and EEG seizures. *Id.* at 46:30–33.

The Specification explains, “[t]he method for treating SE comprises administering to a subject in need thereof an intravenous bolus of ganaxolone in an amount sufficient to suppress SE, which typically is an amount sufficient to produce a ganaxolone plasma concentration of at least 500 ng/ml to about 1000 ng/ml.” *Id.* at 17:32–36. The Specification states:

Typically[,] a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml is sufficient to suppress SE. For example, to achieve a ganaxolone plasma concentration level of 500 ng/ml to about 1000 ng/ml, an infusion of about 5 mg to about 40 mg of ganaxolone can be infused into the subject at the initiation [of] the intravenous bolus. Preferably, about 30 mg of ganaxolone is infused into the subject at the initiation of the intravenous bolus or during the intravenous bolus[.] The intravenous bolus can be administered (i.e., infused) into the subject for about 1 minute to about 5 minutes.

*Id.* at 3:30–42. The Specification defines the term “infusion” as ‘a non-oral administration, typically intravenous’ that “occurs over a longer period than a bolus administration, for example for a time period greater than 1 hour (e.g., from about 1 hour to about 120 hours).” *Id.* at 45:30–35. The Specification defines the term “intravenous bolus” as “a relatively large dose of medication (e.g., ganaxolone) administered in a short period, for example within 1 to 60 minutes (e.g., 3 or 5 minutes).” *Id.* at 45:20–22.

The Specification states that “[c]ontinued suppression of SE is achieved when the continuous infusion maintains a plasma concentration of ganaxolone of about 500 ng/ml or higher throughout a target concentration period.” *Id.* at 3:53–56. The Specification explains that, “[g]enerally, it is desired that the ganaxolone plasma concentration is not higher than about 1000 ng/ml” because a higher concentration “can induce anesthesia, which is not a desired effect of treatment.” *Id.* at 3:65–4:2.

The Specification explains that ganaxolone, 3 $\alpha$ -hydroxy-3 $\beta$ -methyl-5 $\alpha$ -pregnan-20-one, is the subject of an Investigational New Drug Application (IND). *Id.* at 29:39–42. It is a 3 $\beta$ -methylated synthetic analogue of the endogenous neurosteroid allopregnanolone designed to not activate nuclear progesterone receptors. *Id.* at 29:60–66. According to the Specification, “[g]anaxolone provides an alternative mechanism in the treatment of seizures and could serve as effective therapy in the management of SE.” *Id.* at 30:16–18. The Specification describe ganaxolone’s mechanism of action as follows:

Ganaxolone acts as a positive allosteric modulator of  $\gamma$ -aminobutyric acid type A ( $GABA_A$ ) receptors in the CNS. Ganaxolone affects  $GABA_A$  receptors by interacting with a recognition site that is distinct from other allosteric  $GABA_A$  receptor modulators, such as benzodiazepines and barbiturates. Ganaxolone binds to synaptic- and extrasynaptic receptors, mediating both phasic and tonic modulation, respectively. The unique binding of ganaxolone to these two distinct receptor types does not lead to the tolerance seen with benzodiazepines and allows ganaxolone to act as a broad-spectrum GABAergic compound with the potential to treat the myriad of symptoms related to pediatric genetic epilepsies, refractory seizures, cognitive and behavioral disorders, and sleep dysfunction.

*Id.* at 30:1–15 (citations omitted).

*D. Illustrative Claim*

Petitioner challenges claims 1–21 of the ’100 patent. Claim 1, set forth below, is the only independent claim in the ’100 patent and is illustrative of the claimed subject matter.

1. A method of treating status epilepticus (SE), comprising administering to a subject in need thereof an effective amount of ganaxolone to suppress SE, wherein the effective amount of ganaxolone is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours.

Ex. 1001, 57:9–15. Dependent claims 2, 3, and 12 recite aspects of the ganaxolone intravenous bolus. Dependent claims 2–11, 13, 15, 17, and 20 recite aspects of the ganaxolone infusion. Dependent claims 14, 18, 19, and 21 recite that the subject has refractory status epilepticus. Dependent claim 16 recites a range for the total daily dose of ganaxolone.

*E. Asserted Grounds of Unpatentability*

Petitioner asserts that claims 1–21 are unpatentable on the following three grounds:

| Claims Challenged | 35 U.S.C. § <sup>1</sup> | References                                     |
|-------------------|--------------------------|------------------------------------------------|
| 1–21              | 103                      | During <sup>2</sup> , NCT03350035 <sup>3</sup> |

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<sup>1</sup> The Leahy-Smith America Invents Act, Pub. L. No. 112–29, 125 Stat. 284 (2011) (“AIA”), amended 35 U.S.C. § 103, effective March 16, 2013. The earliest claimed priority date for the ’100 is after the effective date of the applicable AIA amendment. *See* Ex. 1001, (60). Accordingly, we apply the AIA version of §103.

<sup>2</sup> Matthew During, US 11,395,817 B2, issued July 26, 2022 (Ex. 1003, “During”).

<sup>3</sup> ClinicalTrials.gov, *Intravenous Ganaxolone as Adjunctive Therapy to Treat Subjects with Status Epilepticus*, NCT03350035, available at <https://clinicaltrials.gov/study/NCT03350035?term=NCT03350035&rank=1>

| Claims Challenged | 35 U.S.C. § <sup>1</sup> | References                                                                                                                             |
|-------------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| 1–21              | 103                      | During, Tsai 2017, <sup>4</sup> Tsai 2016, <sup>5</sup> Clinical Leader 2016 <sup>6</sup>                                              |
| 1–21              | 103                      | During, NCT03350035, Practical Neurology 2019, <sup>7</sup> Ramsay 2019, <sup>8</sup> AES 2019, <sup>9</sup> Husain 2020 <sup>10</sup> |

&lab=hIstory&a=1 (first posted Nov. 22, 2017) (Ex. 1004, “NCT03350035”).

<sup>4</sup> J. Tsai et al., *Phase I Study to Determine the Pharmacokinetics, Pharmacodynamics, and Safety of IV Ganaxolone in Healthy Adults, Final Programme of the 6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures* 74–75 (2017) (Ex. 1005, “Tsai 2017”).

<sup>5</sup> J. Tsai et al., *Phase I Study to Determine the Pharmacokinetics, Pharmacodynamics, and Safety of IV Ganaxolone in Healthy Adults*, 80 *Annals of Neurology* S77–78 (2016) (Ex. 1006, “Tsai 2016”).

<sup>6</sup> ClinicalLeader.com, *Ganaxolone Phase 1 Data Supports Progressing to Phase 2 in Patients with Status Epilepticus*, Clinical Leader (Oct. 19, 2016), <https://www.clinicalleader.com/doc/ganaxolone-phase-dataprogressing-phase-patients-epilepticus-0001> (Ex. 1007, “Clinical Leader 2016”).

<sup>7</sup> Treatment of Refractory Status Epilepticus Prevents Need for Induced Coma with Intravenous Anesthetics in Phase 2 Trial, *Practical Neurology* (Oct. 18, 2019), <https://practicalneurology.com/news/treatment-of-refractory-status-epilepticus-prevents-need-for-induced-coma-with-intravenous-anesthetics-in-phase-2-trial> (Ex. 1010, “Practical Neurology 2019”).

<sup>8</sup> R. Eugene Ramsay et al., *Pharmacokinetic and Pharmacodynamic (PK/PD) Relationship of Intravenous Ganaxolone in Refractory Status Epilepticus* (Nov. 25, 2019), [https://aesnet.org/abstractslisting/pharmacokinetic-and-pharmacodynamic-\(pk/pd\)-relationship-of-intravenous-ganaxolone-in-refractory-status-epilepticus](https://aesnet.org/abstractslisting/pharmacokinetic-and-pharmacodynamic-(pk/pd)-relationship-of-intravenous-ganaxolone-in-refractory-status-epilepticus) (Ex. 1008, “Ramsay 2019”).

<sup>9</sup> R. Eugene Ramsay, *Pharmacokinetic and Pharmacodynamic (PK/PD) Relationship of Intravenous Ganaxolone in Refractory Status Epilepticus*, *Marinus Pharmaceuticals* (Dec. 7, 2019), <https://marinuspharma.com/wp-content/uploads/2020/09/AES-2019-GNX-in-RSE-Ph2-Poster-vFINAL.pdf> (Ex. 1011, “AES Poster 2019”).

<sup>10</sup> A. Husain et al., *Intravenous Ganaxolone Achieves Rapid and Dose-Dependent Sustained Improvement in EEG Seizure Burden in Patients*

Petitioner also relies upon the Declaration of Raman Sankar, M.D., Ph.D. (Ex. 1002). Patent Owner relies upon Declarations, including, Maciej Gasior (Ex. 2001), Henrikas Vaitkevicius, M.D. (Ex. 2002), and Michael A. Rogawski, M.D., Ph.D. (Ex. 2011).

## II. ANALYSIS

### A. *Person of Ordinary Skill in the Art*

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art (“POSA”) at the time the application for the ’100 patent was filed “would have had a medical degree or a Ph.D. in pharmacology or fields related to the development of pharmaceuticals and would have been familiar with the PK [pharmacokinetics] and PD [pharmacodynamics] of pharmaceuticals.” Pet. 18. Additionally, Petitioner asserts “[a] POSA also would have had several years of experience as a practicing neurologist treating patients who suffer from seizure disorders, including SE, and/or several years of experience in researching treatments for such seizure disorders.” *Id.* (citing Ex. 1002 ¶ 50).

According to Patent Owner, a person of ordinary skill in the art at the time the application for the ’100 patent was filed, “would have had a medical degree, or a Ph.D. in pharmacology or other field related to the development of pharmaceuticals, or equivalent degree, and several years of

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*with Refractory Status Epilepticus*, Poster Abstract F53, 37 J. CLIN. NEUROPHYSIOLOGY 332 (July 2020) (Ex. 1009, “Husain 2020”).

experience as a practicing neurologist treating patients who suffer from seizure disorders including status epilepticus and/or several years of experience in researching treatments for such seizure disorders.” Prelim. Resp. 17–18 (citing Ex. 2011 ¶ 44).

We note that the parties’ proposed definitions are largely similar, except that Patent Owner additionally recognizes “an equivalent degree” as an alternative to a medical degree or Ph.D. in pharmacology or other field related to the development of pharmaceuticals. *Compare* Pet. 18 *with* Prelim. Resp. 17–18. We do not need to resolve this issue as our findings and conclusion in this Decision would be the same under either proposed definition.

#### *B. Claim Construction*

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b); 37 C.F.R. § 100(b). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). “In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17).

Petitioner asserts that the claim phrase “to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml” recited in claim 1 should be construed as nonlimiting. Pet. 18. According to

Petitioner, that claim phrase has no bearing on the claimed method, as the claim already recites that the method comprises administering “an effective amount of ganaxolone to suppress SE” and that such amount is “administered as an intravenous bolus plus continuous infusion.” *Id.* In support of this position, Petitioner offers the testimony of Dr. Sanker, who states:

To determine what amount of ganaxolone is effective to suppress SE, a POSA would have administered ganaxolone as a bolus followed by continuous infusion and then monitored the patient’s electroencephalography (“EEG”) activity to confirm the suppression of SE. A POSA would have understood that the claimed plasma concentration (i.e., “about 500 ng/ml to about 1000 ng/ml”) does not further limit “an effective amount of ganaxolone to suppress SE.” Therefore, the recited plasma concentration adds nothing to these steps and is superfluous.

Ex. 1002 ¶ 56. According to Petitioner and Dr. Sanker, “a POSA would have understood that it is the end result (i.e., suppression of SE) that defines the amount of ganaxolone administered, meaning the claimed plasma concentration (i.e., “about 500 ng/ml to about 1000 ng/ml”) does not change the method of the claims and is superfluous.” Pet. 19 (citing Ex. 1002 ¶ 56). Moreover, Petitioner asserts that its claim interpretation is “consistent with the ’100 patent’s specification, which links ‘effective amount’ with SE suppression” by explaining that “[d]uring the treatment, the subject can be monitored for plasma concentration of neurosteroid (e.g. ganaxolone) and using EEG for seizure activity. If the subject appears to show signs of SE relapse, the amount of ganaxolone administered can be adjusted accordingly.” *Id.* at 20 (quoting Ex. 1001, 17:6–11). According to Petitioner, this statement in the Specification “confirms that whether an effective amount of ganaxolone has been administered to suppress SE is determined

by monitoring EEG for seizure activity and adjusting the ganaxolone dose, as needed.” *Id.* (citing Ex. 1002 ¶ 58).

Patent Owner asserts that the challenged claim phrase should be construed as limiting because the pharmacokinetic parameters recited in that phrase were “explicitly relied on by both Applicant and the Examiner to distinguish over the prior art and thus support patentability over the prior art.” Prelim. Resp. 20. Additionally, Patent Owner asserts that the “it is evident from the claim language itself that the PK parameters recited . . . give ‘meaning and purpose to the manipulative step’ because it relates back to how the ‘effective amount’ must be administered and what it must do.” *Id.* at 20–21.

According to Patent Owner, “the ‘effective amount’ required by claim 1 must be ‘effective’ to *both* ‘suppress SE’ *and* ‘produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours.’” *Id.* at 21 (quoting claim 1). In this regard, Patent Owner asserts the Specification demonstrates that “[w]hile all dosing regimens (“low,” “medium,” and “high” dose cohorts) described in Example 3 were able to suppress SE for a period of time, only the “high” dose cohort resulted in the claimed plasma concentrations ( $\geq 500$  ng/ml for about 8 hours).” *Id.* (citing Ex. 1001, Fig. 15; Ex. 1016, Fig. 2).

Based upon our review of the arguments and an examination of the claim language itself, the written description, and the prosecution history, we determine that the record supports finding that the entire “wherein” clause recited in independent claim 1 is limiting. This clause recites,

wherein the effective amount of ganaxolone is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours.

Ex. 1001, 57:11–15. Petitioner does not dispute that this wherein clause requires the ganaxolone to be administered as an intravenous bolus plus continuous infusion. *See* Pet. 18–21. Rather, it is Petitioner’s contention that the wherein clause recitation that such administration is not required “to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours.” *See id.* at 18. According to Petitioner, because the claim first recites that the method of treating status epilepticus comprises “administering to a subject in need thereof an effective amount of ganaxolone to suppress SE,” the wherein clause does not present an additional limitation, as a person of ordinary skill in the art would have monitored a patient’s EEG activity, and not the ganaxolone plasma concentration to determine “an effective amount of ganaxolone to suppress SE.” *Id.* at 19.

Based on our review, the Specification does not support Petitioner’s proposed interpretation. Indeed, the descriptions in the Specification relied upon by Petitioner suggest that an effective amount of ganaxolone is evidenced by monitoring *both* EEG for seizure activity *and* plasma concentration. For example, Petitioner refers to the following passage in the ’100 Specification:

During treatment, the subject can be monitored for plasma concentration of neurosteroid (e.g. ganaxolone) and using EEG for seizure activity. If the subject appears to show signs of SE relapse, the amount of ganaxolone administered can be adjusted accordingly.

Pet. 20 (quoting Ex. 1001, 17:6–11). Petitioner also refers to the following Specification statement:

Electroencephalogram (EEG) can be used to detect signs of SE re-lapse. Plasma concentration of ganaxolone can alternatively or in combination with EEG be used to detect signs of SE re-lapse or a subject that experience SE re-lapse.

*Id.* (citing Ex. 1001, 23:64–24:1). Referring to these disclosures, Petitioner asserts that the Specification “confirms that whether an effective amount of ganaxolone has been administered to suppress SE is determined by monitoring EEG for seizure activity and adjusting the ganaxolone dose, as needed.” *Id.* We disagree. The former disclosure explicitly describes monitoring plasma concentration of ganaxolone and using EEG for seizure activity, Ex. 1001, 17:6–11, and the latter disclosure explicitly describes use plasma concentration “in combination with” EEG to detect signs of SE relapse. These descriptions, in view of the Specification as a whole, support finding that an effective amount of ganaxolone may be determined by considering *both* EEG activity and plasma concentration.

Further, we find that Patent Owner has shown persuasively that Example 3 in the Specification demonstrates how some dosing regimens may be able to suppress SE initially would not provide an amount that is effective to provide a plasma concentration in the range recited, i.e., “of about 500 ng/ml to about 1000 ng/ml,” for the recited period of time, i.e., “for about 8 to about 12 hours.” *See* Prelim. Resp. 21. Example 3 in the Specification describes a Phase 2 Open-Label Dose Range Study with a primary objective “to establish that IV ganaxolone was safe and effective when added to standard of care IV AED [anti-epileptic drug] therapy in stopping SE and preventing the escalation of treatment to IV anesthesia for

seizure suppression.” Ex. 1001, 54:59–62. The study divided the enrolled patients among three dosing cohorts: a low dose cohort (500 mg/day IV ganaxolone); a medium dose cohort (650 mg/day IV ganaxolone); and a high dose cohort (713 mg/day IV ganaxolone). *Id.* at 55:4–12. As Patent Owner asserts, the Specification demonstrates that while SE was suppressed for a time in all patients following ganaxolone treatment, only those receiving the high dose cohort exhibited a plasma concentration of ganaxolone  $\geq 500$  ng/ml for about 8 hours, which was coextensive with sustained suppression of SE. Prelim. Resp. 21 (citing Ex. 1001, Fig. 15); *see also* Ex. 1001 55:13–56:30.

Accordingly, for at least the above-discussed reasons, we are persuaded that the “wherein” clause of independent claim 1 is limiting as it does not simply express an intended result of administering an effective amount of ganaxolone to suppress SE, but is material to patentability.

*C. Obviousness over During and NCT03350035*

Petitioner asserts that claims 1–21 would have been obvious over the combined teachings of During and NCT03350035. Pet. 36–48. Patent Owner disagrees. Prelim. Resp. 36–46.

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). “An obviousness determination requires finding both ‘that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.’” *CRFD*

*Research, Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016)). Obviousness grounds must be supported with “articulated reasoning with some rational underpinning” and not by “mere conclusory statements.” *See KSR Int’l Co.*, 550 U.S. at 418.

*1. During*

During is directed to methods of using allosteric modulators, e.g., ganaxolone, to treat epileptic disorders, including status epilepticus. Ex. 1003, 1:24–33, 4:16, 8:11–14. During teaches that ganaxolone can be administered in doses ranging from 10 mg/kg to 2000 mg/kg. *Id.* at 8:14–34. During describes a study to evaluate the ability of drugs, including ganaxolone, to block benzodiazepine-resistant status epilepticus in male Sprague Dawley rats. *Id.* at 35:31–37:15 (Example 3). The subjects were administered of ganaxolone intraperitoneally at dosages of 0.5 mg/kg, 2 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg. *Id.* at 36:22–24. During explains there was a significant improvement in protection against seizure activity at a dosage of 20 mg/kg. *Id.* at 37:10–11. Independent claim 21 of During recites a method of treating SE comprising administering intravenously to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof. *Id.* at 40:9–13. Claims 24–30 of During recite ranges for the dosage of ganaxolone between 150 mg/day to 1000 mg/day. *Id.* at 40:19–32.

*2. NCT03350035*

NCT03350035 details a plan for a clinical trial study evaluating the effectiveness and safety of investigation drug, intravenous ganaxolone, as adjunctive therapy to treat subjects with SE. Ex. 1004, 1, 3. The study sponsor is listed as Marinus Pharmaceuticals. *Id.* at 1. The study status, as of

November 2017, is reported as “[n]ot yet recruiting.” *Id.* at 2. The plan describes the experimental arm for IV ganaxolone active as “[g]anaxolone IV loading dose with continuous infusion (maintenance dose) for 2-4 days followed by a 24-hour taper.” *Id.* at 3.

### 3. Discussion

Petitioner asserts that “During’s Example 3 evaluates ganaxolone’s ability to block benzodiazepine-resistant SE and shows that 20 mg/kg ganaxolone provides significant improvement in seizure protection.” Pet. 37 (citing Ex. 1003, 35:33–35; Ex. 1002 ¶ 100). Petitioner asserts also that claims 24–31 of During recite methods of treating SE by administering dosages of ganaxolone ranging from 150 mg to 1000 mg/day, including “about 700 mg to 725 mg/day.” *Id.* (citing Ex. 1003, 40:18–33; Ex. 1002 ¶ 100). Further, Petitioner alleges that it was known in the art at the time of the invention that 1,500 mg/day of ganaxolone administered orally was effective for reducing partial-onset seizure frequency. *Id.* (citing Ex. 1023,<sup>11</sup> 561, 562; Ex. 1002 ¶ 101).

According to Petitioner, a skilled artisan “would have been motivated to target even lower doses based on ganaxolone’s oral administration because a POSA would have known that ganaxolone administered intravenously would have higher bioavailability than ganaxolone administered orally.” *Id.* at 38 (citing Ex. 1002 ¶ 101; Ex. 1034,<sup>12</sup> 222). In

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<sup>11</sup> Syndi Seinfeld et al., *Status Epilepticus*, Additional Perspectives on Epilepsy: The Biology of a Spectrum Disorder (Cold Spring Harbor Laboratory Press, 2016, ed. Gregory L. Holmes and Jeffrey L Noebels) (Ex. 2023, “Seinfeld”).

<sup>12</sup> Geoffrey M. Currie, *Pharmacology, Part 2: Introduction to Pharmacokinetics*, 46 J. Nuclear Med. Tech. 221–30 (2018)

particular, Petitioner asserts that the skilled artisan would have motivated “to select a lower dose within the range of 600 to 1,500 mg/day to suppress SE, such as During’s disclosed doses of 625-725 mg/day or 1025-1050 mg/day ganaxolone.” *Id.* (citing Ex. 1002 ¶ 101).

Petitioner asserts that NCT03350035 describes a protocol for evaluating adjunctive IV ganaxolone in subjects with SE by “administering ganaxolone as an ‘IV loading dose with continuous infusion (maintenance dose) for 2-4 days followed by a 24-hour taper.’” *Id.* (quoting Ex. 1004, 3–4; citing Ex. 1002 ¶ 102). According to Petitioner, the combined teachings of During and NCT03350035 would have motivated a person of skill in the art to administer an effective amount of ganaxolone as an IV bolus followed by continuous IV infusion to suppress SE. *Id.* at 38–41 (citing Ex. 1002 ¶ 104). Additionally, Petitioner asserts a skilled artisan would have had a reasonable expectation that combining the dosing regimen of NCT03350035 with the doses in During would successfully suppress SE and it would have been routine for the artisan to have optimized the dose administered to suppress SE. *Id.* at 41–42 (citing Ex. 1002 ¶ 112).

Further, Petitioner contends that if the ganaxolone plasma concentration limitation of claim 1 is given patentable weight, a skilled artisan “would have understood that “the doses of ganaxolone in the prior art that provide an effective amount of ganaxolone to suppress SE would necessarily result in the ganaxolone plasma concentration limitation of claim 1.” *Id.* at 42 (citing Ex. 1002 ¶¶ 112–115; Ex. 1003, 7:40–8:8, 8:11–34). According to Petitioner, “the ganaxolone plasma concentration

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(Ex. 1034, “Currie 2018”).

limitation is the ‘natural result flowing from’ the administration of an effective amount of ganaxolone to suppress SE and is inherent.” *Id.*

Patent Owner contends, among other things, that neither During, NCT03350035, nor any combination thereof, teach or suggest the wherein clause of claim 1, i.e., “wherein the effective amount of ganaxolone is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours.” Prelim. Resp. 42. In particular, Patent Owner asserts that Petitioner’s reliance on inherency for the recited ganaxolone plasma concentration and duration fails because Petitioner has not demonstrated that this limitation would necessarily be achieved with the dosing taught by the prior art. *Id.* at 43. Patent Owner asserts that Petitioner and Dr. Sankar have not even identified “which doses or dosing regimens of ganaxolone a POSA would have selected (other than, generically, those ‘described in the prior art that provide an effective amount of ganaxolone to suppress SE’), or any other evidence why the resulting PK values would necessarily have occurred.” *Id.* at 45–46 (citing Pet. 42; Ex. 1002 ¶ 115). According to Patent Owner, the Specification provides evidence to the contrary, as it “shows that the plasma concentration levels and durations recited in the claims do not necessarily result from the dose ranges in the art (e.g. the low dose cohort in the Phase 2 trial).” *Id.* at 46.

Having considered the arguments and the evidence on the record, we agree with Patent Owner that Petitioner has not shown sufficiently for institution that the claimed invention would have been obvious over the combined teachings of During and NCT03350035. As discussed above, in Section II.B., we have determined that the “wherein” clause of independent claim 1 is liming. In other words, the claim requires that the effective

amount of ganaxolone is administered as an IV bolus plus continuous infusion and that such administration produces and maintains a ganaxolone plasma concentration of about 500 to 1000 ng/ml for about 8 to 12 hours. With respect to the recited plasma concentration limitation, Petitioner has alleged only that it is met inherently. Dr. Sankar has only offered the same conclusory position in his declaration. *See* Ex. 1002 ¶¶ 113, 115.

While “inherency may supply a missing claim limitation in an obviousness analysis,” this doctrine “must be carefully circumscribed in the context of obviousness.” *PAR Pharmaceutical, Inc. v. TWI Pharmaceuticals, Inc.*, 773 F.3d 1186, 1194–1195 (Fed. Cir. 2014). As the Federal Circuit has explained:

The mere fact that a certain thing may result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

*Id.* at 1195 (quoting *In re Oelrich*, 666 F.2d, 578, 581 (C.C.P.A. 1981).

Here, Petitioner and Dr. Sankar have not explained or demonstrated why or how the natural result of administering the dosages in During according to the method disclosed in NCT03350035 would produce and maintain a ganaxolone plasma concentration of about 500 to 1000 ng/ml for about 8 to 12 hours. This deficit is more pronounced in view of the Specification disclosure of a Phase 2 Open-Label Dose Range Study that exemplifies how some ganaxolone dosages that suppressed SE did not produce and maintain ganaxolone plasma concentrations  $\geq 500$  ng/ml for about 8 to 12 hours. *See* Ex. 1001, Fig 15; *see also* Ex. 1001, 55:13–56:30. Thus, because Petitioner relies on inherency for the plasma concentration limitation without providing

evidence that such inherency exists, Petitioner has failed to establish sufficiently for institution that During and NCT03350035 teach or suggest each limitation of the claim 1.

Accordingly, we determine that Petitioner has not shown a reasonable likelihood of prevailing in its obviousness challenge of independent claim 1 or its dependent claims 2–21 over During and NCT03350035.

*D. Obviousness over During and the Marinus Phase I Clinical Trial Results Reported in Tsai 2017, Tsai 2016, and Clinical Leader 2016*

Petitioner asserts that claims 1–21 would have been obvious over the combined teachings of During and the Marinus Phase I Clinical Trial Results Reported in Tsai 2017, Tsai 2016, and Clinical Leader 2016. Pet. 48–53.

Patent Owner disagrees. Prelim. Resp. 46–50. We incorporate our description and discussion of During in Section II.C. here.

*1. Tsai 2017*

Tsai 2017 is a detailed printed program for the 6<sup>th</sup> London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures. Ex. 1005, 1. The program includes a poster abstract for the “Phase 1 study to determine the pharmacokinetics, pharmacodynamics, and safety of IV ganaxolone in healthy adults.” *Id.* at 74. The study consisted of six cohorts. *Id.* Patients were “assessed following a single bolus and bolus dosing following by continuous infusion of GNX IV. The PK from each cohort was modeled to select the doses for subsequent cohorts.” *Id.* Tsai 2017 explains that “[t]reatment emergent adverse effects were mild in severity and resolved without intervention.” *Id.* at 74–75. Tsai 2017 states that “GNX concentrations in plasma were generally proportional to the administered dose,” and “[p]otential anti-convulsant plasma concentrations were achievable with a bolus dose.” *Id.* at 75. Tsai 2017 concluded that “GNX

administered as a rapid IV bolus or bolus with continuous infusion was generally safe and well tolerated; there were no safety issues that limit getting to a potentially efficacious plasma concentration in a short period of time.” *Id.* Additionally, Tsai 2017 concluded that “[p]redictable PK from this study enables dosing guidance for GNX IV.” *Id.*

## 2. *Tsai 2016*

Tsai 2016 is a printed program from the American Neurological Association (ANA) for their 2015 Annual Meeting. Ex. 1006. The program contains an abstract describing the objectives and parameters of the “Phase 1 Study to Determine the Pharmacokinetics, Pharmacodynamics, and Safety of IV Ganaxolone in Healthy Adults” discussed in Tsai 2017. Ex. 1006, 77. This abstract explains what will be administered, evaluated and determined in the study. *Id.* at 77–78. The abstract explains that the results of the Phase 1 Study will be presented at the time of the meeting. *Id.*

## 3. *Clinical Leader Report*

Clinical Leader Report is an online newsletter sourced from Marinus Pharmaceuticals and announcing that “Ganaxolone Phase 1 Data Supports Progressing To Phase 2 In Patients With Status Epilepticus.” Ex. 1007, 1–2. This reference reports the results of the Phase 1 study, similar to Tsai 2017. *Id.* at 1 Clinical Leader Reports disclosed that the study was “designed to determine the pharmacokinetics (PK), pharmacodynamics (PD), and safety of ganaxolone IV administered as an ascending bolus dose (Stage 1) or continuous infusion (Stage 2).” *Id.* “Every dose regimen of ganaxolone IV administered either bolus or continuous infusion was generally safe and well tolerated and reached targeted dose levels in a short period of time.” *Id.*

#### 4. Discussion

Petitioner again relies on During as disclosing a method of treating SE by administering ganaxolone at doses ranging from about 500 mg to 1000 mg/day. Pet. 48. Petitioner refers to the additional references, Tsai 2017, Tsai 2016, and Clinical Leader Report, as “Marinus’s Phase I CTRs,” i.e., Marinus’s Phase 1 Clinical Trial Results. *Id.* According to Petitioner, these references “each describe the results of a phase 1 study to evaluate the safety, PK, and PD of ganaxolone administered as a bolus dose and continuous infusion to healthy participants.” *Id.*

In particular, Petitioner asserts that Tsai 2017: (a) “reports the Phase 1 pharmacokinetic results as showing that ganaxolone plasma concentrations were generally proportional to the administered dose;” (b) “concludes that ganaxolone ‘administered as a rapid IV bolus or bolus with continuous infusion was generally safe and well tolerated;” and (c) “[p]redictable PK from this study enables dosing guidance for [ganaxolone] IV.” *Id.* (quoting Ex. 1005, 75). According to Petitioner, “these disclosures demonstrate that there was nothing unpredictable about dosing ganaxolone as a bolus followed by continuous infusion,” and that a POSA would have been motivated to administer an effective amount of ganaxolone in this matter to suppress SE and to optimize the dose when doing so. *Id.* at 48–49 (citing Ex. 1002 ¶¶ 138–141).

Additionally, Petitioner asserts that a skilled artisan would have had a reasonable expectation of successfully suppressing SE in this manner because Marinus’s Phase 1 CTRs found that ganaxolone plasma concentrations were ‘generally proportional to the administered dose’ and that ‘[p]otential anti-convulsant plasma concentrations were achievable with a bolus dose.’” *Id.* at (quoting Ex. 1005, 75; citing Ex. 1007, 1, Ex. 1002

¶¶ 147–154).

Patent Owner argues, among other things, that “Petitioner relies on an incorrect claim construction that reads the PK parameters of the ‘wherein’ clause out of the claim” and that “Petitioner offers no arguments at all under the correct claim construction.” Prelim. Resp. 48–49. Further, Patent Owner contends that none of the references relied upon by Petitioner teach or suggest a treatment method using ganaxolone to suppress SE “wherein the effective amount of ganaxolone is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 hours to about 12 hours,” as required by claim 1. *Id.* at 49.

Having considered the arguments and evidence on the record, we agree with Patent Owner that Petitioner has not sufficiently shown for institution that During, Tsai 2017, Tsai 2016, and Clinical Leader 2016, alone or in combination, teach or suggest the limitations of the “wherein” clause of claim 1. As discussed above, in Section II.B., we have determined that the “wherein” clause of independent claim 1 is limiting. In other words, the claim requires that the effective amount of ganaxolone is administered as an IV bolus plus continuous infusion and that such administration produces and maintains a ganaxolone plasma concentration of about 500 to 1000 ng/ml for about 8 to 12 hours.

As Patent Owner contends, for this ground, Petitioner has not applied the correct construction of claim 1 or even addressed it. Specifically, Petitioner has not asserted or argued how the relied upon art provides a method that achieves and maintains the recited plasma concentration for the recited duration. Indeed, based upon our review of the record, we do not find any teaching or suggestion for this claim element in the cited art. Insofar as

Petitioner may have intended to repeat the inherency argument raised in the first ground, we have explained above how that inherency argument is unpersuasive.

Accordingly, we determine that Petitioner has not shown a reasonable likelihood of prevailing in its obviousness challenge of independent claim 1 or its dependent claims 2–21 over the combination of During, Tsai 2017, Tsai 2016, and Clinical Leader 2016.

*E. Obviousness over During, NCT03350035, and the Phase 2 Clinical Trial Results Reported in Practical Neurology 2019, Ramsay 2019, AES 2019, and Husain 2020*

Petitioner asserts that claims 1–21 would have been obvious over the combined teachings of During, NCT03350035, and the Phase 2 Clinical Trial Results Reported in Practical Neurology 2019, Ramsay 2019, AES 2019, and Husain 2020. Pet. 53–58. Patent Owner disagrees. Prelim. Resp. 23–36. We incorporate our description and discussion of During and NCT03350035 in Section II.C. here.

*1. Discussion*

For this obviousness ground, Petitioner relies on During and NCT03350035 in a similar manner as discussed above for the first ground of obviousness. *See* Pet. 53. Petitioner refers to the additional references, i.e., Practical Neurology 2019, Ramsay 2019, AES 2019, and Husain 2020, as “the Phase 2 CTRs.” *Id.* Petitioner relies on the Phase 2 CTRs for their description of the Phase 2 clinical trial results for treating RSE by administering ganaxolone. *Id.*

The parties dispute the priority date of the ’100 patent. Petitioner acknowledges that the four Phase 2 CTRS are prior art only if the ’100 patent claims are not entitled to the priority date of the provisional

application. *See id.* 32–33. Patent Owner contends that Petitioner’s ground fails “because the four Phase 2 Clinical Trial references are not prior art to the Challenged Claims.” Prelim. Resp. 23. We agree with Patent Owner.

The application that issued as the ’100 patent, serial number 17/186,569, was filed on February 26, 2021, as a continuation of international application number PCT/US2020/044843, filed on August 4, 2020, which in turn claims the benefit of U.S. Provisional Application No. 62/882,648,<sup>13</sup> filed on August 5, 2019. Ex. 1001, codes (21), (22), (60), (63), 1:5–9. The parties’ priority dispute centers on whether the ’648 provisional application includes written description support sufficient to show possession of the limitation in independent claim 1 reciting that the effective amount of ganaxolone is administered “to produce and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for 8 hours to about 12 hours.” *See* Pet. 21; Prelim. Resp. 25; Ex. 1001, 57:11–15.

As the Federal Circuit has explained, “for a patent’s claims to be entitled to an earlier priority date, the patentee must demonstrate that the claims meet the requirements of 35 U.S.C. § 120.” *In re NTP, Inc.*, 654 F.3d 1268, 1276 (Fed. Cir. 2011) (citations omitted). Those requirements include the written-description requirement of Section 112. *See* 35 U.S.C. § 120.

The test for written description “requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The “level of detail required to satisfy the written

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<sup>13</sup> U.S. Provisional Application No. 62/882/648 (and excerpts of file history), filed August 5, 2019 (Exhibits 1031 and 2018, “’648 provisional application”).

description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Id.* However, “the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). “In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms., Inc.*, 598 F.3d 1336, 1351.

Based on our consideration of the arguments and evidence, we determine that the ’648 provisional application conveys with reasonable clarity to those skilled in the art that Applicant/Patent Owner was in possession of the claimed invention as of the provisional filing date. *See Hyatt v. Dudas*, 492 F.3d 1365, 1370 (Fed. Cir. 2007).

As Patent Owner explains, the ’648 provisional application includes initial data from the results of the Marinus Phase 2 clinical trial. Specifically, Example 2 in the provisional application contains the heading “PRELIMINARY CLINICAL EVIDENCE OF EFFICACY IN SUBJECTS WITH STATUS EPILEPTICUS” and describes Example 2 as “an ongoing, double-blind, randomized, placebo-controlled Phase 2 study designed to evaluate the safety, tolerability, and efficacy of adjunctive IV GNX in subjects with SE who have failed initial treatment with benzodiazepines and at least one AED.” Ex. 2018, Example 2. In this example, the provisional application sets forth pharmacokinetic modeling data from the five subjects enrolled in the study and relays that such data “suggested that exposure levels of GNX at approximately 1000 ng/ml were associated with rapid and completed SE suppression, and lower GNX exposures at <500 ng/mL were

associated with seizure relapse.” *Id.* ¶ 188. Indeed, the provisional application reports that “all 5 subjects showed immediate cessation of SE with the initiation of initial bolus plus continuous infusion dose” and that “[s]eizure activity relapsed when plasma concentrations of GNX decreased < 500 ng/mL in 4 out of 5 subjects.” *Id.* ¶¶ 189, 203. From those disclosures, we agree with Patent Owner and its expert, Dr. Rogawski, that a skilled artisan would have considered Applicant to have had possession of treating patients suffering from SE by administering ganaxolone as a bolus plus continuous infusion to “produce and maintain a plasma concentration of about 500 ng/ml to about 100 ng/ml” at the time that the provisional application was filed. *See* Prelim. Resp. 27–28; Ex. 2011 ¶ 58.

Patent Owner also demonstrates persuasively that the ’648 provisional application describes possession of the claimed duration for maintaining a plasma concentration in the recited range, i.e., “for about 8 hours.” For this claim element, Patent Owner directs us to the disclosure in the provisional application explaining that “the United States Food and Drug Administration (FDA) allowed the daily limit of Captisol exposure to increase to 50 g/day (and the total daily dose of GNX to increase from 500 to 715 mg), *thereby allowing for GNX exposure to be maintained at >500 ng/ml for approximately 8 hours.*” Ex. 2018 ¶ 203 (emphasis added). Captisol is the solubilizing agent used for the ganaxolone formulation used in the clinical trial. *See* Prelim. Resp. 8 (citing Ex. 2011 ¶ 51, Ex. 1001, 48:9–12). As Patent Owner’s expert explained, “[b]ecause ganaxolone was formulated in a fixed ratio with Captisol[], the daily limit on Captisol[] effectively limited the amount of ganaxolone that could be administered per day. Ex. 2011 ¶ 51.

The provisional application describes how the ganaxolone dosing protocol was amended with the increased daily limit of Captisol, and reports

that one subject was treated with the dosing regimen designed to administer ganaxolone to provide and maintain a plasma concentration at > 500 ng/ml for approximately 8 hours. Ex. 2011 ¶¶ 203–204. The provisional application discloses that “[w]ithin 3 minutes after starting the IV GNX infusion, the [refractory SE] ceased and seizure protection was maintained for the remaining 48 hours of GNX treatment.” *Id.* ¶ 204.

Petitioner acknowledges the disclosures in Example 2 of the provisional application, yet argues that because the application states that “[p]harmacokinetic data were unavailable at the time of this report” for the subject that was treated with the amended dosing protocol, the application lacked data that “would have demonstrated to a POSA that the ganaxolone plasma concentration was maintained ‘at least about 500 ng/ml for at least about 8 to about 12 hours’ in this single patient.” Pet. 23–24 (citing Ex. 1002 ¶¶ 64–66). We disagree.

As discussed above, the ’648 provisional application disclosed “[s]eizure activity relapsed when plasma concentrations of GNX decreased < 500 ng/mL in 4 out of 5 subjects.” Ex. 2018 ¶¶ 189, 203. The provisional application also discloses that the protocol was amended to allow “GNX exposure to be maintained at >500 ng/ml for approximately 8 hours.” *Id.* ¶ 203. Then, the provisional application exemplifies that “seizure protection was maintained” for the duration of the ganaxolone infusion, which exceeded 8 hours and encompassed 12 hours. *Id.* ¶ 204. We determine that, taken together, these disclosures clearly allow a skilled artisan to recognize that the inventor invented what is claimed.

Because we find that the ’648 provisional application describes sufficiently the elements of the challenged claims, including the disputed concentration and duration limitations, we determine that the claims are

entitled to the benefit of the '648 provisional application. Thus, Petitioner has not established that the Phase 2 CTRs are prior art in view of the August 5, 2019 priority date.

Accordingly, we determine that Petitioner has not demonstrated a reasonable likelihood of establishing that it would prevail in showing the unpatentability of claims 1–21 over the asserted combination that relies upon the disclosures of the Phase 2 CTRs.

*F. Discretion under 35 U.S.C. § 325(d)*

Patent Owner requests that the Board exercise its discretion under 35 U.S.C. § 325(d) to deny institution because the same or substantially the same prior art or arguments were previously presented to the Office. Prelim. Resp. 54–61. Petitioner argues that discretionary denial is not warranted. Pet. 59–60. Because we deny institution on the merits, we do not reach Patent Owner's § 325(d) argument.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has not established a reasonable likelihood of prevailing in its assertion that at least one challenged claim of the '100 patent is unpatentable. Accordingly, we deny the Petition and decline to institute the requested *inter partes* review.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied*, and no trial is instituted.

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Patent 11,110,100 B2

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