

Marinus Pharmaceuticals, Inc. v. Ovid Therapeutics, Inc.

PGR2023-00020
May 22, 2024, Oral Hearing
Petitioner's Presentation

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Overview

- Patent Owner (“PO”), recognizing the overbreadth of its claims, has disclaimed most of the challenged claims.
- Claims 1-21, 23, and 24 were disclaimed at POPR
- The remaining Challenged Claims (22 and 25-31) are broader than PO alleges; the Board properly found that they cover more than just human patients.
- PO’s claims are anticipated and obvious over Petitioner’s prior work which teaches treating Status Epilepticus (SE) with ganaxolone—including at the doses and having the effects recited in the challenged claims
- PO cannot use unexpected results of Petitioner’s studies to avoid obviousness as the ’817’s claims are broad and not commensurate in scope with unexpected results from Petitioner’s specific dosing regimen.

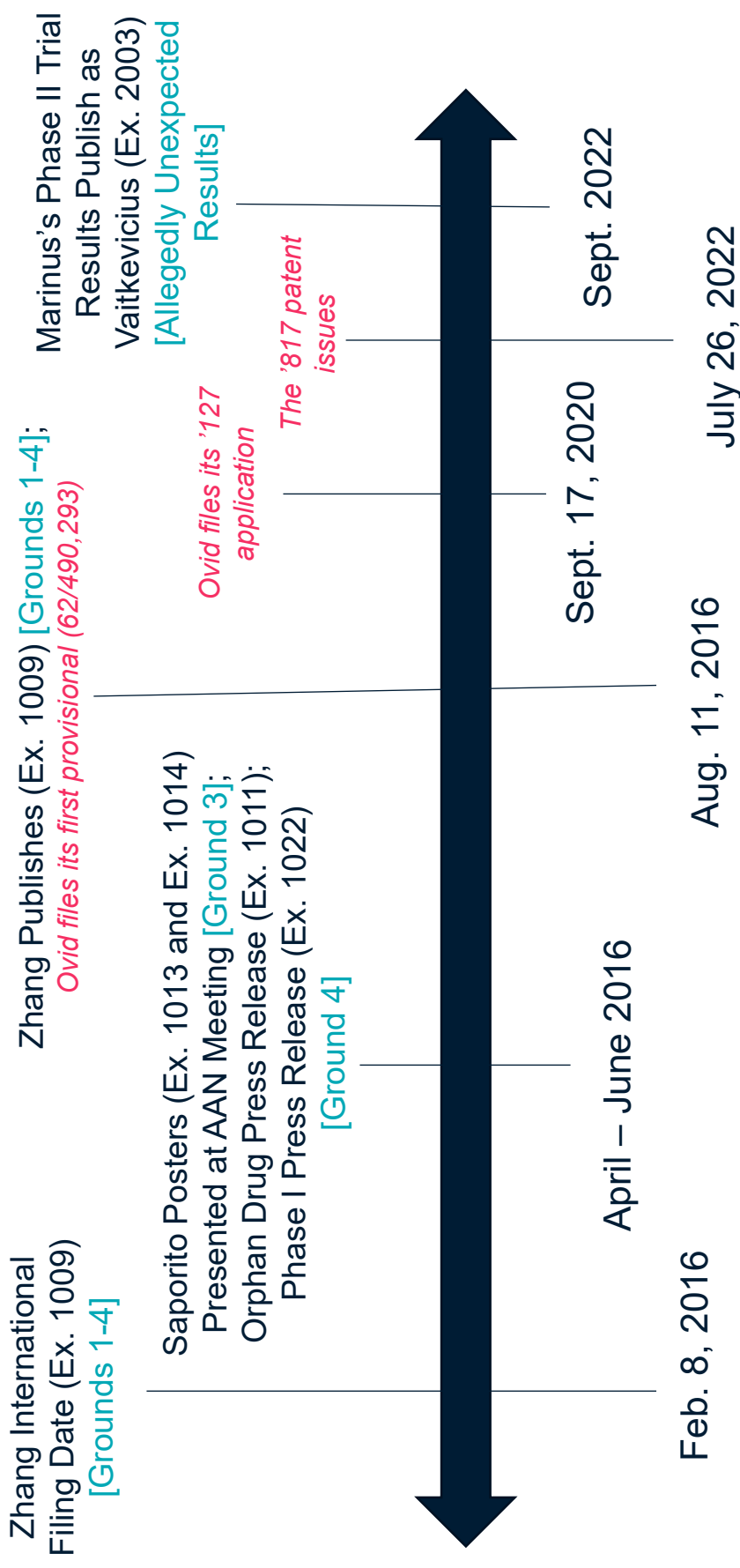
Remaining Grounds

Ground	Claims	Basis for Rejection
1	22, 25-31	Anticipation by Zhang (Ex. 1009)
2	22, 25-31	Obviousness over Zhang
3	22, 25-31	Obviousness over Zhang and Saporito P1 (Ex. 1013) and/or Saporito P2 (Ex. 1014)
4	22, 25-31	Obviousness over Zhang, Marinus's Orphan Drug Press Release (Ex. 1011), and Marinus's Phase I Press Release (Ex. 1022)
7	22, 25-31	Lack of enablement

Petition at 4; Reply at 3



PO's Claims are Anticipated or Obvious over Marinus Publications – Because Petitioner Did the Work, and Did it First



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Disclaimed Claims 1-20

1. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof.
2. The method of claim 1, wherein the patient is administered ganaxolone or a pharmaceutically acceptable salt thereof twice daily.
3. The method of claim 1, wherein the patient is administered ganaxolone or a pharmaceutically acceptable salt thereof three times daily.
4. The method of claim 1, wherein the pharmaceutical composition is an oral suspension.
5. The method of claim 1, wherein the pharmaceutical composition is an oral capsule.
6. The method of claim 4, wherein the patient is administered ganaxolone or a pharmaceutically acceptable salt thereof in an amount of up to 1,800 mg/day.
7. The method of claim 1, wherein the pharmaceutical composition is an oral suspension comprising 50 mg/ml ganaxolone or a pharmaceutically acceptable salt thereof.
8. The method of claim 1, wherein the pharmaceutical composition is an oral suspension comprising 50 mg/ml ganaxolone or a pharmaceutically acceptable salt thereof and is administered three times daily.
9. The method of claim 1, wherein the pharmaceutical composition is an oral suspension comprising 50 mg/ml ganaxolone or a pharmaceutically acceptable salt thereof administered three times daily wherein the patient is administered an amount of up to 1,800 mg/day.
10. The method of claim 1, wherein the patient is administered 600 mg ganaxolone or a pharmaceutically acceptable salt thereof.
11. The method of claim 1, wherein the patient is administered 600 mg ganaxolone or a pharmaceutically acceptable salt thereof three times daily.
12. The method of claim 1, wherein the patient is administered 50 mg ganaxolone or a pharmaceutically acceptable salt thereof.
13. The method of claim 1, wherein the patient is administered 100 mg ganaxolone or a pharmaceutically acceptable salt thereof.
14. The method of claim 1, wherein the patient is administered 200 mg ganaxolone or a pharmaceutically acceptable salt thereof.
15. The method of claim 1, wherein the patient is administered 300 mg ganaxolone or a pharmaceutically acceptable salt thereof.
16. The method of claim 1, wherein the patient is administered 400 mg ganaxolone or a pharmaceutically acceptable salt thereof.
17. The method of claim 1, wherein the patient is administered 500 mg ganaxolone or a pharmaceutically acceptable salt thereof.
18. The method of claim 1, wherein the patient is administered oral capsules comprising 200-600 mg ganaxolone or a pharmaceutically acceptable salt thereof.
19. The method of claim 1, wherein the pharmaceutical composition provides reduction in the frequency of seizures.
20. The method of claim 1, wherein the pharmaceutical composition provides reduction in the frequency of seizures, the severity of seizures, or a combination thereof.

Ex. 1001 at Claims 1-21, 23, and 24

Petition at 28-31

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Disclaimed Claims 21, 23, and 24

21. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof wherein the pharmaceutical composition is administered intravenously.

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23. The method of claim 21 wherein the pharmaceutical composition comprises about 30 mg ganaxolone.

24. The method of claim 21 wherein the patient is administered about 150 mg to 1000 mg/day ganaxolone.

Ex. 1001 at Claims 1-21, 23, and 24
Petition at 28-31

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DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Remaining Challenged Claims: 22 and 25-31

21. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof wherein the pharmaceutical composition is administered intravenously.

22. The method of claim 21 wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.

25. The method of claim 21 wherein the patient is administered about 500 mg to 1000 mg/day ganaxolone.

26. The method of claim 21 wherein the patient is administered about 625 mg to 650 mg/day ganaxolone.

27. The method of claim 21 wherein the patient is administered about 650 mg to 675 mg/day ganaxolone.

28. The method of claim 21 wherein the patient is administered about 675 mg to 700 mg/day ganaxolone.

29. The method of claim 21 wherein the patient is administered about 625 mg to 700 mg/day ganaxolone.

30. The method of claim 21 wherein the patient is administered about 700 mg to 725 mg/day ganaxolone.

31. The method of claim 21 wherein the patient is administered about 1025 mg to 1050 mg ganaxolone.



US 11,395,817 B2

(16) Patent No.: US 11,395,817 B2
(45) Date of Patent: Jul. 26, 2022

ABSTRACT

US 11,395,817 B2

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Claim Construction

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

“Patient in Need Thereof” is Not Limited to Humans

21. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof wherein the pharmaceutical composition is administered intravenously.

Petitioner:

The '817 defines “patient” (used interchangeably with “subject”) as “includ[ing], but not limited to, primates such as humans, canines, porcine, ungulates, rodents, poultry, and avian.”¹²⁷ One such patient within the scope of the Challenged Claims is, therefore, a rat.¹²⁸ Another is a human.¹²⁹

Patent Owner:

“Treating status epilepticus comprising administering to a patient in need thereof” in claims 22 and 25-31 means “treating a human patient suffering from SE.”

Ex. 1001 at Claims 21, 22, 25-31

Petition at 34-35; POPR at 27

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The '817 Explicitly Defines its Patients as including Animals . . .

“Patient” and “subject” are used interchangeably herein and include, but not limited to, primates such as humans, canines, porcine, ungulates, rodents, poultry, and avian.

. . . Animals That Suffer From Status Epilepticus, Just Like Humans:

(porcine), or rat (rodent). Perhaps Ovid assumes that there would be no practical use of the claimed inventions of the '817 patent in species other than humans. This assumption completely ignores the entire veterinary market. (*See* Sankar Deposition Transcript, Ex. 1042, at page 88, line 20 to page 92, line 14). A veterinarian's patient is just as much a patient as a medical doctor's patient, and veterinarians routinely treat their animal patients for SE using medications! (*See*,

FISH Ex. 1001 at 32:65-67; Ex. 1041 at ¶ 22
Petition at 34-35; Reply at 5-7

The Board's Analysis in the Institution Decision was Correct

While a term in a Specification may be interpreted by implication, we are not persuaded by Patent Owner's attempt to infer a different construction that contradicts the express definition of "patient" and "subject" in the '817 patent. Patent Owner simply asserts that a skilled artisan would understand someone in need of treatment of status epilepticus to be solely a human patient, and provides no evidentiary basis to exclude veterinary uses of the compound, particularly when the '817 patent expressly defines the term "patient" to include such veterinary patients.

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Institution Decision at 9

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DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

The Doses Recited in Claims 25-31 Are Not Suitable Only for Human Patients

while the very largest, including the Newfoundland and the St. Bernard, can weigh over 200 lbs.”). That the specific doses set forth in claims 25–31 may be higher than the dose that would likely be given to a rat does not suggest to a person of skill in the art that the term “patient” in the claims is limited to humans. Those doses could apply to any number of species that are also covered by the ’817 patent’s definition of “patient.”]

Ex. 1041 at ¶ 30
Reply at 5-7

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DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

“Improvement . . . After Administration For More Than 8 Hours” (Claim 22)

22. The method of claim 21 wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.

Patent Owner:

“Improvement to the patient after administration for more than 8 hours” in claim 22 means that there is improvement to the human patient more than 8 hours after the full dose of ganaxolone is given, regardless of whether the full amount of ganaxolone is given in a single administration or multiple administrations. Ex. 2014, ¶ 65.

Petitioner:

The '817 patent explains that “improvement” refers to a relative change in symptoms, which may be measured “in a subject prior to treatment, and again one or more times after treatment is initiated.”²³ *Initiated*, not completed. This is consistent with how those in clinical practice measure improvement during treatment.²⁴

POR at 24; Reply at 7-8

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“Improvement . . . After Administration For More Than 8 Hours” (Claim 22)

’817 Patent (Ex. 1001)

“Improvement” refers to the treatment of symptoms or conditions associated with epileptic disorders, measured relative to at least one symptom or condition of the metabolic disease.

An effective amount or therapeutically effective amount can be a dosage sufficient to treat, inhibit, or alleviate one or more symptoms of an epileptic disorder such as reducing the frequency or severity of seizures, reducing behavior abnormalities (or otherwise improving behavior); or to provide a desired pharmacologic and/or physiologic effect, for example, reducing, inhibiting, or reversing one or more of the underlying pathophysiological mechanisms underlying the neurological dysfunction, increasing dopamine levels or signaling, or a combination thereof. The precise dosage will

FISH Ex. 1041 at ¶¶ 38-39; Ex. 1001 at 29:57-60, 9:17-26
POR at 24-25; Reply at 7-8, 9-11

Measuring Improvement After Treatment *Initiation* Is Consistent with the Intrinsic Record and Clinical Practice

Dr. Rogawski (Ex. 1041)

34. Indeed, measuring an improvement at intervals after *initiation* of treatment is consistent with how improvement is measured in clinical practice when SE is treated. Patients exhibiting SE are critically ill and they are monitored closely and continuously for changes in their condition after the start of treatment, not only after a treatment ends.

36. In fact, this is how ganaxolone was dosed and how improvement was measured in Marinus's clinical trials, as show, for example, in the *Epilepsia* publication (Ex. 2003). In the study described in this publication, improvement was measured both after initiation (at 24 hours, while continuous infusions were ongoing—rows 1 and 2) and after completing an entire dosing regimen (relapse during 24 h following infusion completion, row 3) (Table 2).

'817 Patent (Ex. 1001)

In embodiments, the methods described herein are effective to reduce, delay, or prevent one or more other clinical symptoms of an epileptic disorder, such as acute repetitive seizures. For example, the effect of a gaboxadol or a pharmaceutically acceptable salt thereof, and/or an allosteric modulator or a pharmaceutically acceptable salt, derivative or analogue thereof, on a particular symptom, pharmacologic, or physiologic indicator can be compared to an untreated subject, or the condition of the subject prior to treatment. In embodiments, the symptom, pharmacologic, and/or physiologic indicator is measured in a subject prior to treatment, and again one or more times after treatment is initiated. In embodiments, the control is a reference level, or average determined based on measuring the symptom, pharmacologic, or physiologic indicator in one or more subjects that do not have the disease or condition to be treated (e.g., healthy subjects). In embodiments, the effect of the treatment is compared to a conventional treatment that is known the art.

FISH Ex. 1001 at 9:43-16; Ex. 2003; Ex. 1041 at ¶¶ 34-36
POR at 24; Reply at 7-8

Ovid Changes the Claim Language

Claim language:

22. The method of claim 21 wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.

Ovid's language:

The plain and ordinary language of claim 22 requires there to be improvement to the patient for more than 8 hours *after administration* of the amount of ganaxolone required to treat SE. While the claim language allows for that total amount of

65. A POSA would have understood the phrase “improvement to the patient after administration for more than 8 hours” as used in claim 22 to mean improvement to the human patient 8 hours after the full dose of ganaxolone is given, regardless of whether the dose of ganaxolone is given in a single administration or multiple administrations.

FISH Ex. 1001 at claim 22; Ex. 2014 at ¶ 65
POR at 24

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Zhang (Ex. 1009) Anticipates Claim 22

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

All of PO's Expert Opinions Depend on the Wrong Claim Construction – And Can Be Rejected on That Basis Alone

Ovid (POR):

VI. Ground 1: Zhang Does Not Anticipate Claims 22 and 25-31

A. Zhang does not describe “treating status epilepticus comprising administering to a patient in need thereof” from claims 22 and 25-31

Claims 22 and 25-31 depend from claim 21, which recites “administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof wherein the pharmaceutical composition is administered intravenously.” Under the proper construction, “treating status epilepticus comprising administering to a patient in need thereof” requires treating a *human* patient suffering from SE. See *supra* § V.A. Petitioner, however, points to nothing in Zhang that describes treating a human patient, let alone one suffering from SE. Pet., 35-38; Ex. 2014, ¶ 70. Petitioner cites only to paragraphs [0005] and

Dr. Sankar (Ex. 1042):

Q. You say, “A POSA would have understood that the phrase treating status epilepticus comprising administering to a patient in need thereof in claims 22 and 25 to 31 means, quote, treating a human patient suffering from SE,” end quote. Do you see that?

A. Yes.

Q. So all of your opinions are based upon that interpretation of the claims?

A. Yes.

Ex. 1042 at 42:8-43:1
POR at 25:8-28:10; Reply at 8

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Claim 22 of the '817 Patent relates to Improvement 8 Hours after Administration

	21. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof
	wherein the pharmaceutical composition is administered intravenously.
	22. The method of claim 21 wherein the pharmaceutical composition provides
	improvement to the patient after administration for more than 8 hours.

Ex. 1001 at Claims 21, 22
POR at 25:8-28:10; Reply at 8



Zhang (Ex. 1009)

[0029] The disclosure provides injectable substituted β -cyclodextrin ganaxolone formulations, including formulations containing CAPTISOL-ganaxolone inclusion complexes. Injectable substituted β -cyclodextrin ganaxolone formulations disclosed herein include formulations suitable for intramuscular, intravenous, intraarterial, intraspinal, and intrathecal injection. Injectable formulations include parenteral formulations suitable for intravenous infusion.

METHODS OF TREATMENT

[0069] The disclosure includes methods of treating status epilepticus, refractory status epilepticus, super-refractory status epilepticus, PCDH19 female pediatric epilepsy, and other seizure disorders comprising administering an effective amount of the substituted β -cyclodextrin-ganaxolone injectable formulation to a patient suffering from any of these seizure disorders

[0022] A “patient” is a human or non-human animal in need of medical treatment. Medical treatment includes treatment of an existing condition, such as a disorder or injury. In certain embodiments treatment also includes prophylactic or preventative treatment, or diagnostic treatment

Ex. 1009 at ¶¶ [0022], [0029], [0069]; see also Ex. 1003 at ¶¶ 61-63
Petition at 35-38, 43; Reply at 8-9

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Zhang Teaches the Method of Now Disclaimed Claim 21, Which Claim 22 Depends Upon

	21. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof
	wherein the pharmaceutical composition is administered intravenously.
	22. The method of claim 21 wherein the pharmaceutical composition provides improvement to the patient after administration for more than 8 hours.

The Data in Zhang’s Example 8 Demonstrates the Inherent Result

Drug Treatment Groups

[0126] TABLE 4 presents the drug treatment group used in this study. All injections were via jugular vein catheter except in those animals in which the jugular vein catheter became clogged. These animals were injected via the tail vein.

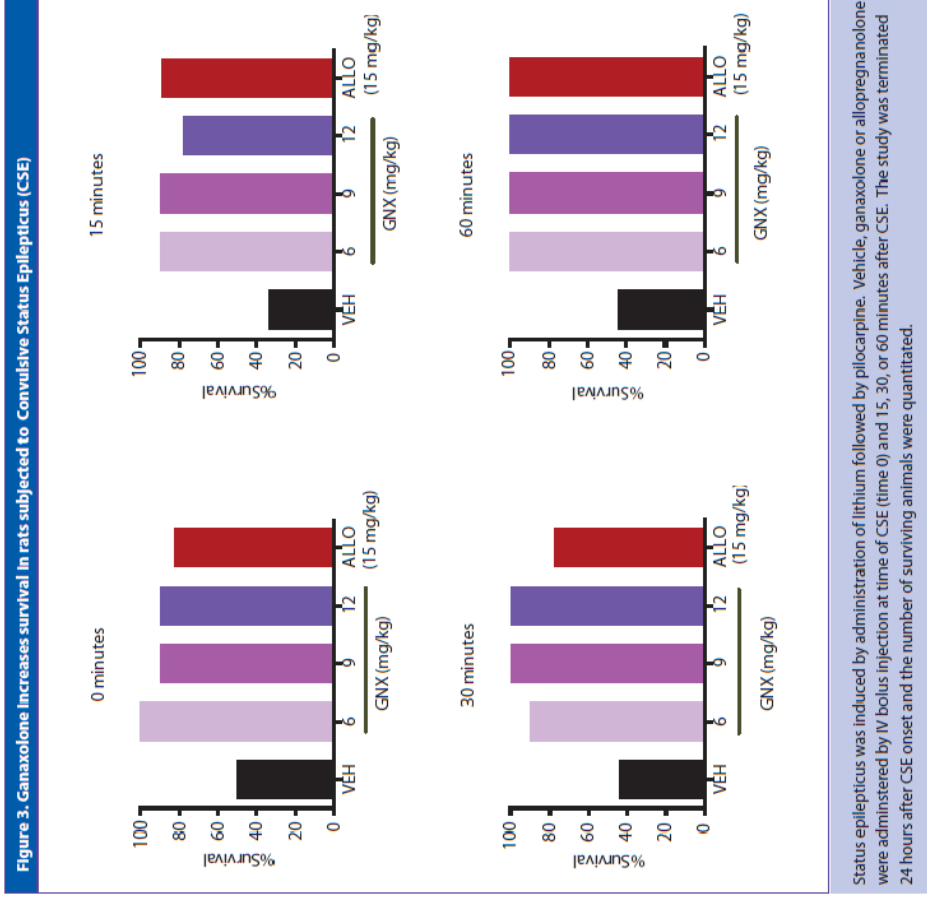
TABLE 4				
Parameter	Vehicle	Allopregnanolone	GNX	GNX
Dosage (mg/kg)	0	15 mg/kg	12mg/kg	15 mg/kg
Vehicle	30% Captisol/ water	30% Captisol/ water	30% Captisol/ water	30% Captisol/ water
Drug (mg/ mL)	0	2.5	2.5	2.5
Parameter	Vehicle	Allopregnanolone	GNX	GNX
Dose volume (mL/ kg)	6	6	4.8	6
Time of administrations after seizure onset (minutes)	15' or 60'	15' or 60'	15' or 60'	15' or 60'

Ex. 1009 at Example 8; see also Ex. 1003 at ¶¶ 93-94
Petition at 45; Reply at 10

Saporito Poster 1 (Ex. 1013) Shows Improvement in 24-hour Survival

Dr. Rogawski:

[0127]. In the experiments presented in Saporito Poster 1, rats were treated intravenously with ganaxolone in the same manner as Zhang (including intravenously at a dose of 12 mg/kg) but were *not* sacrificed at five hours. As shown in Figure 3 of the Saporito Poster (excerpted below), rats receiving a single bolus IV administration of ganaxolone at all doses (including the 12 mg/kg dose) administered at all time points after SE onset (including 15 and 60 minutes after SE onset) exhibited markedly increased rates of survival at 24-hours compared to vehicle, such that nearly all animals survived. (Ex. 1013, Methods, Figure 3, Conclusions). Thus, there was dramatic improvement after eight hours whether this is assessed after initiation or completion of treatment administration.



Ex. 1013; Ex. 1041 at ¶ 49
 Petition at 45; Reply at 10-11

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The '817 Patent Itself Shows Improvement in 24-hour Survival

Institution Decision:

F.3d 1373, 1377 (Fed. Cir. 2003). In this case, Zhang demonstrates that ganaxolone continues to improve status epilepticus in rats for 5+ hours, supporting the inherency position. Moreover, the '817 patent's Specification shows that 10 and 20 mg/kg ganaxolone doses that bracket the 12 and 15 mg/kg ganaxolone doses tested by Zhang, result in improved 24-hour survival relative to lower doses. See Ex. 1001, Fig. 4; Ex. 1009, 21 ¶ 117. This evidence further supports Petitioner's inherency position because it shows that doses bracketing those recited in Zhang provide continued improvement to patients for periods exceeding 8 hours. "Extrinsic evidence can be used to demonstrate what is 'necessarily present' in a prior art embodiment even if the extrinsic evidence is not itself prior art." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020).



Ex. 1001 at Example 3 (35:31-37:15)
Institution Decision at 27

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

TABLE 2

Overall survival and protection results			
Compound (dose, mg/kg)	Protection (includes PK rats)	24-hour Survival (excludes PK rats)	
VEH (40% HPBCD)	0/13 (0%)	8/11* (72%)	
ALLO (0.5 mg/kg)	0/13 (0%)	6/10 (60%)	
GBD (0.5 mg/kg)	2/13 (15%)	7/10 (70%)	
GNX (0.5 mg/kg)	0/13 (0%)	6/10 (60%)	
ALLO (2 mg/kg)	0/13 (0%)	7/10 (70%)	
GBD (2 mg/kg)	0/13 (0%)	8/10 (80%)	
GNX (2 mg/kg)	0/13 (0%)	8/10 (80%)	
ALLO (5 mg/kg)	0/13 (0%)	7/9 (72%)	
GBD (5 mg/kg)	0/13 (0%)	6/11* (55%)	
GNX (5 mg/kg)	0/13 (0%)	7/10 (70%)	
ALLO (10 mg/kg)	2/13 (15%)	9/10 (90%)	
GBD (10 mg/kg)	0/13 (0%)	10/10 (100%)*	
GNX (10 mg/kg)	1/13 (7.7%)	9/10 (90%)	
ALLO (20 mg/kg)	1/13 (7.7%)	9/10 (90%)	
GBD (20 mg/kg)	0/13 (0%)	7/9 (78%)	
GNX (20 mg/kg)	4/13 (30.8%)*	9/10 (90%)	

*Significantly different from VEH, p < 0.05
#Spontaneous death during SE in PK group rat 110 min post -SE onset, but sample was collected.

PO's Expert Agrees that Increased 24-Hour Survival is an Improvement

Dr. Sankar (Ex. 1042)

THE WITNESS: It's pretty common that we want to know how many rats survived. We know lithium pilocarpine has significant mortality associated with it. So in a study pertaining to treatment, if you increase survival that will be a beneficial outcome in treatment.

Ex. 1042 at 37:12-21
Reply at 10-11

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DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

“Improvement After 8 Hours” is an Inherent Result of the Methods Described in Zhang

Finally, we address Bristol’s argument that new uses of old processes are patentable, that we should treat the expressions of efficacy as limitations be-

cause they distinguish the new use of the process over the prior art, and that claims should be read to preserve their validity.

Bristol is correct that new uses of known processes may be patentable. See 35

However, the claimed process here is not directed to a new use; it is the same use, and it consists of the same steps as described by Kris. Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent. *In re May*, 574 F.2d

Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc., 246 F.3d 1368, 1376 (Fed. Cir. 2001)
Petition at 44-45; Reply at 9-11

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Zhang (Ex. 1009) Data Shows Treatment Effects At Tested Doses For 2 Hours Or More

TABLE 7 - Treatment Effects, Rats Treated 60 minutes post SE onset							
		Significance, Time post drug administration					
Comparison	Frequency	0-15 min.	15-30	30-60	1-2 hrs	2-3 hrs	3-5 hrs
Vehicle vs. Allo.(15 mg/ml), both administered 15' post SE onset	0-5 Hz	**	ns	Ns	ns	ns	ns
	5-10 Hz	**	ns	Ns	ns	ns	ns
	10-30 Hz	ns	ns	Ns	ns	ns	ns
	30-50 Hz	ns	ns	Ns	ns	ns	ns
	50-70 Hz	ns	ns	Ns	ns	ns	ns
	70-96 Hz	ns	ns	Ns	ns	ns	ns
Vehicle vs GNX (12 mg/ml) both administered 15 minutes post SE onset	0-5 Hz	***	****	****	****	***	**
	5-10 Hz	****	****	****	***	**	ns
	10-30 Hz	*	**	**	**	*	ns
	30-50 Hz	ns	ns	*	**	*	ns
	50-70 Hz	ns	*	**	**	*	ns
	70-96 Hz	ns	**	***	***	**	ns

Ex. 1009 ¶ 136



Zhang (Ex. 1009) – Demonstrated Improvement in Rats with SE, Which Were Sacrificed at 5 Hours

EXAMPLE 8. GANAXOLONE EFFECT ON PILOCARPINE-INDUCED STATUS EPILEPTICUS IN RATS

[0117] This study was designed to determine the ability of a CAPTISOL-ganaxolone (GNX) formulation administered intravenously (IV) at 12 and 15 mg/kg to inhibit pilocarpine induced status epilepticus (SE). Allopregnanolone (Allo) (15 mg/kg; IV) was also evaluated for comparison. In this study, test drugs were administered either 15 or 60 minutes after onset of SE and compared to vehicle (30% Captisol).

Seizure Induction, Treatment, and Recording Protocol

[0127] The animals were evaluated in 3 consecutive daily sessions. The experimental schedule is shown in TABLE 5. The time of SE onset was determined by observation and recorded, and the animal dosed with the vehicle, allopregnanolone, or ganaxolone either 15 or 60 min post SE-Onset. Rats were observed for behavior changes at approximately 2, 15, 30, 60, 120 and 240 minutes after pilocarpine administration. Each animal was recorded once and euthanized 5 h after treatment.

[0134] Ganaxolone at 12 and 15 mg/kg produced qualitatively similar results, with both dose levels producing a very strong reduction in SE amplitude overall.

Ex. 1009 at ¶¶ [0117]-[0136], see also Ex. 1003 at ¶¶ 89-95; Ex. 1041 at ¶¶ 42-49
Petition at 44-45; Reply at 9-11

FISH.

Multiple Doses Provides Sustained Treatment for More Than 8 Hours

[0070] Seizure disorders that may be treated with the substituted β -cyclodextrin-ganaxolone injectable formulation include status epilepticus, e.g., convulsive status epilepticus, e.g., early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus, e.g., super-refractory generalized status epilepticus; non-convulsive status epilepticus, e.g., generalized status epilepticus, complex partial status epilepticus, a seizure, e.g., acute repetitive seizures, cluster seizures, infantile spasms, Lennox-Gastaut syndrome, West syndrome, PCDH19 female pediatric epilepsy, and catamenial epilepsy.

[0074] Methods of treatment include treating a patient suffering from seizures, traumatic brain injury, or stroke by administering a single injection (bolus dose) of a substituted β -cyclodextrin-ganaxolone injectable formulation. The single injection may be administered intramuscularly or intravenously. The dose of the single injection may be from about 1 mg/kg to about 20 mg/kg, from about 2 mg/kg to about 15 mg/kg, from about 2 mg/kg to about 10 mg/kg, or about 2 mg/kg to about 8 mg/kg. Methods of treatment also include administering multiple injections of the β -cyclodextrin-ganaxolone injectable formulation over a period of 1 to 10 days. The injections may be given at intervals of 1 to 24 hours. Dosing schedules in which the substituted β -cyclodextrin-ganaxolone injectable formulation is injected every 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs, 12 hrs, or 24 hours are included herein. Dosing schedules in which the substituted β -cyclodextrin-ganaxolone injectable formulation is injected for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days are included herein.

Ex. 1009 at ¶¶ [0070]-[0074], Ex. 1003 at ¶ 94
Petition at 45; Reply at 10

FISH.

Reduction in Seizures During First 5 Hours After Administration Provides Improvement After 8 Hours

Dr. Rogawski (Ex. 1041)

41. Furthermore, improvement for a limited period of time (e.g., for five hours) reduces overall risk of a worse outcome at later times (e.g., at eight hours or more). For example, initial or transient improvement provides an opportunity for natural healing (such as clearing of a brain infection by the immune system), time for a curative treatment (such as an antibiotic) to be administered, or time for patients to be transferred to a facility that can provide a greater level of care. Any of these would provide improvement in the overall risks of adverse consequences of SE (such as brain damage, permanent disability, and death) at eight hours and beyond.

40. I have noted previously in this declaration that SE is a severe life-threatening medical emergency, which is associated with a high risk of permanent neurological damage and death. As a physician attempting to treat SE during its dynamic and evolving course over minutes and hours, I would consider any degree of improvement at any time point to be clinically worthwhile even if the extent of improvement is of a lesser degree than had been obtained at a different point in treatment.

48. And what is more, as I described above, even transient improvement (e.g., during the first five hours, as demonstrated in Zhang's Example 8) provides an improvement in the overall risks of adverse consequences of SE (such as brain damage, permanent disability, and death) at eight hours and beyond.

Ex. 1041 at ¶¶ 40-49; see also Ex. 1042 at 19:22-20:15
Petition at 44-45; Reply at 9-11

FISH.

“Improvement After 8 Hours” is an Inherent Result of the Methods Described in Zhang

improvement to the patient after administration for more than 8 hours.”¹⁷⁴ While Zhang does not expressly disclose that its ganaxolone formulations provide “improvement to the patient after administration for more than 8 hours,” this would be the natural result of administering them to a patient with SE, as taught by Zhang.¹⁷⁵ As such, Zhang inherently teaches the limitation of claim 22.

Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc., 246 F.3d 1368, 1376 (Fed. Cir. 2001)
Petition at 44-45; Reply at 9-11

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Zhang Anticipates Claim 22

	21. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof
	wherein the pharmaceutical composition is administered intravenously.
	22. The method of claim 21 wherein the pharmaceutical composition provides
	improvement to the patient after administration for more than 8 hours.

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Claim 22 Would Have Been Obvious

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Grounds 2, 3, and 4: Obviousness

Ground	Claims	Basis for Rejection
 1	22,	Anticipation by Zhang (Ex. 1009)
2	22,	Obviousness over Zhang
3	22,	Obviousness over Zhang and Saporito P1 (Ex. 1013) and/or Saporito P2 (Ex. 1014)
4	22,	Obviousness over Zhang, Marinus's Orphan Drug Press Release (Ex. 1011), and Marinus's Phase I Press Release (Ex. 1022)
7	22,	Lack of enablement

Zhang Alone Provides the POSA with a Reasonable Expectation of Success at Achieving the Claimed Methods of Treating SE with Ganaxolone (Ground 2)

108. Based on the teachings in Zhang, those of skill in the art would have had a reasonable expectation of success in achieving the claimed methods. As discussed above in Section IV, the rat lithium-pilocarpine model was, and is, a widely accepted model to identify potential treatments for SE. Example 8 of Zhang teaches that IV-administered ganaxolone terminates SE, i.e., ganaxolone gave a positive result in the model.

Ex. 1003 at ¶ 106-109
Petition at 48-49

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DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Rat Pilocarpine Model Translates to Humans

A B S T R A C T

The pilocarpine animal model of status epilepticus is a well-established, clinically translatable model that satisfies all of the criteria essential for an animal model of status epilepticus: a latency period followed by spontaneous recurrent seizures, replication of behavioural, electrographic, metabolic, and neuropathological changes, as well as, pharmacoresistance to anti-epileptic drugs similar to that observed in human status epilepticus. However, this

31. It is recognized in the field that the rat pilocarpine model and the related rat lithium-pilocarpine model are both translationally relevant models for identifying treatments for SE, in part because “studies have found similar electrophysiological and morphological abnormalities in the rat hippocampus of the pilocarpine model of SE ... and human SE.” (Imtiyaz, Ex. 1006, at 2 (citing sources).)

Ex. 1006 at 1; 1003 at ¶ 31

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The Saporito Posters Are § 102(a)(1) Prior Art

- “The statutory phrase ‘printed publication’ has been interpreted to mean that **before the critical date** the reference must have been **sufficiently accessible** to the **public interested in the art**”
 7. One of the Marinus posters, entitled “Ganaxolone Administered Intravenously Prevents Behavioral Seizures and Promotes Survival in the Rat Lithium-Pilocarpine Model of Status Epilepticus” was part of Poster Session II at the meeting on Sunday, April 17. The listing of this Poster (referred to hereafter as “Saporito Poster 2”), entitled “Intravenous Administration of Ganaxolone Attenuates Electroencephalographic Seizures in a Diazepam Resistant Model of Status Epilepticus,” was part of Poster Session IV at the meeting on Tuesday, April 19. On
 5. The AAN Annual Meeting is an annual gathering of several thousand clinicians and researchers with an interest in current topics and research on various subjects in neurology. It is attended by both clinicians practicing in neurology and researchers interested in looking for potential new treatments for neurological disorders. I would consider it to be an important and influential gathering in the neurology field, and I attend it regularly. The AAN Meeting Brochure describes the Annual Meeting as “the place to discover the very latest, groundbreaking research across a wide variety of neurology topics.” (AAN Meeting Brochure at 7.) As someone who has attended these meetings, I agree with that description.

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Ex. 1015 (Declaration of Dr. Michael Saporito)
Petition at 5-7

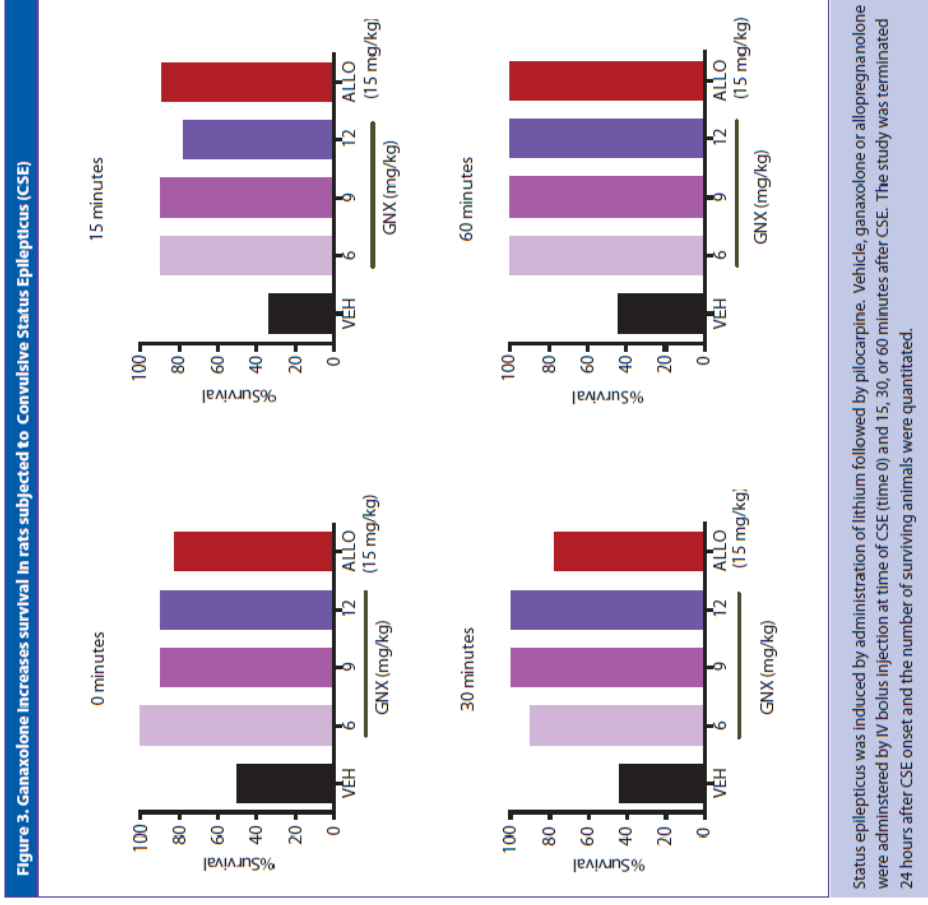
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DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Saporito Poster 1 (Ex. 1013) Shows Improvement in 24-hour Survival

Dr. Rogawski:

[0127]. In the experiments presented in Saporito Poster 1, rats were treated intravenously with ganaxolone in the same manner as Zhang (including intravenously at a dose of 12 mg/kg) but were *not* sacrificed at five hours. As shown in Figure 3 of the Saporito Poster (excerpted below), rats receiving a single bolus IV administration of ganaxolone at all doses (including the 12 mg/kg dose) administered at all time points after SE onset (including 15 and 60 minutes after SE onset) exhibited markedly increased rates of survival at 24-hours compared to vehicle, such that nearly all animals survived. (Ex. 1013, Methods, Figure 3, Conclusions). Thus, there was dramatic improvement after eight hours whether this is assessed after initiation or completion of treatment administration.



FISH. Ex. 1013; Ex. 1041 at ¶ 49
Petition at 45; Reply at 10-11

The Saporito Posters Provide Additional Experimental Evidence (Ground 3)

Dr. Rogawski:

58. As I have noted, Zhang Example 8 and the results presented in the Saporito posters provide strong and convincing evidence of a treatment effect. Considering how expansively the '817 patent defines “treating” provides further support that a POSA would have a reasonable expectation that administering ganaxolone will provide a treatment effect in a human.

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Ex. 1003 at ¶¶ 110-121; Ex. 1041 at 51-58
Petition at 50-57; Reply at 15-17

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DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

The Marinus Press Releases Provide Additional Evidence of Obviousness (Ground 4)

Dr. Rogawski:

60. As I previously noted, a POSA would have known that to obtain Orphan Drug Designation, the FDA Office must have concluded that there was sufficient “information about the drug, or the disease or condition for which it is intended to *establish a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treating of that disease or condition.*” (First Declaration, Ex. 1003, para. 125).

61. Also as previously noted, a POSA would have understood that for the FDA to allow a Phase I trial to commence, that it has determined that IV ganaxolone was reasonably likely to be successful in the treatment of SE in humans. (First Declaration, Ex. 1003, para. 126).

Ex. 1003 at ¶¶ 122-128; Ex. 1041 at 59-61
Petition at 50-57; Reply at 15-17

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Zhang (Ex. 1009) Anticipates Claims 25-31

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Claims 25-31 of the '817 Patent are Anticipated

	21. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof wherein the pharmaceutical composition is administered intravenously.
	25. The method of claim 21 wherein the patient is administered about 500 mg to 1000 mg/day ganaxolone.
	26. The method of claim 21 wherein the patient is administered about 625 mg to 650 mg/day ganaxolone.
	27. The method of claim 21 wherein the patient is administered about 650 mg to 675 mg/day ganaxolone.
	28. The method of claim 21 wherein the patient is administered about 675 mg to 700 mg/day ganaxolone.
	29. The method of claim 21 wherein the patient is administered about 625 mg to 700 mg/day ganaxolone.
	30. The method of claim 21 wherein the patient is administered about 700 mg to 725 mg/day ganaxolone.
	31. The method of claim 21 wherein the patient is administered about 1025 mg to 1050 mg ganaxolone

Zhang Teaches Doses of 1-20 mg/kg per Day

[0085] The disclosure includes embodiments in which multiple bolus doses of the ganaxolone/ sulfobutyl ether- β -cyclodextrin formulation are administered to the patient. In certain embodiments the multiple bolus doses are given over 1 to 10 days at intervals of 1 to 24 hours. In certain embodiments each bolus dose provides a sufficient amount of ganaxolone to produce a plasma $C_{\max}$ of ganaxolone of about 100 ng/ mL to about 1000 ng/ mL in the patient. In certain embodiments the interval between bolus doses is from about 10 to about 24 hours and once an initial $C_{\max}$ is reached the plasma concentration of ganaxolone is not below 100 ng/ mL at any time between bolus doses. In certain embodiments the interval between bolus doses is 20 to 24 hours and once an initial $C_{\max}$ is reached and the concentration of ganaxolone in the patient's plasma does not fall below 25% of the initial $C_{\max}$. In certain embodiment each bolus dose comprises about 1 mg/kg to about 20 mg/kg ganaxolone. Or, optionally the single bolus dose comprises from about 2 mg/kg to about 15 mg/kg ganaxolone, or about 4 mg/kg to about 10 mg/kg ganaxolone, or from about 1 mg/kg to about 30 mg/kg ganaxolone.

Ex. 1009 at ¶ 85
Petition at 46-48; Reply at 11-12

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Zhang’s 1-20 mg/kg Dose Range Encompasses Those of Claims 25-31

Claim(s)	Amount Administered Per Day (range in mg)	Amount Administered to a 70 kg Patient Per Day (range in mg/kg)
24	150–1000	2.14–14.29
25	500–1000	7.14–14.29
26	625–650	8.93–9.29
27	650–675	9.29–9.64
28	675–700	9.64–10
29	625–700	8.93–10
30	700–725	10–10.36
31	1025–1050	14.64–15

initial C_{max} . In certain embodiment each bolus dose comprises about 1 mg/kg to about 20 mg/kg ganaxolone. Or, optionally the single bolus dose comprises from about 2 mg/kg to about 15 mg/kg ganaxolone, or about 4 mg/kg to about 10 mg/kg ganaxolone, or from about 1 mg/kg to about 30 mg/kg ganaxolone.

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Ex. 1003 at ¶¶ 103-104; Ex. 1009 at ¶ 85
Ineos USA LLC v. Berry Plastics, Corp. 783 F.3d 865, 869 (Fed. Cir. 2015)
Petition at 47-48

Zhang Anticipates Claims 25-31

F.2d 775, 782 (Fed.Cir.1985). If the prior art discloses its own range, rather than a specific point, then the prior art is only anticipatory if it describes the claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over the ranges. *Atofina*, 441 F.3d at 999; *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed.Cir.2012). Limitation 2 is

Ineos USA LLC v. Berry Plastics Corp., 783 F.3d 865, 869 (Fed. Cir. 2015)
Petition at 47-48

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Zhang Anticipates Claims 25-31 of the '817 Patent

	21. A method of treating status epilepticus comprising administering to a patient in need thereof a pharmaceutical composition comprising ganaxolone or a pharmaceutically acceptable salt thereof wherein the pharmaceutical composition is administered intravenously.
	25. The method of claim 21 wherein the patient is administered about 500 mg to 1000 mg/day ganaxolone.
	26. The method of claim 21 wherein the patient is administered about 625 mg to 650 mg/day ganaxolone.
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	29. The method of claim 21 wherein the patient is administered about 625 mg to 700 mg/day ganaxolone.
	30. The method of claim 21 wherein the patient is administered about 700 mg to 725 mg/day ganaxolone.
	31. The method of claim 21 wherein the patient is administered about 1025 mg to 1050 mg ganaxolone

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Claims 25-31 Would Have Been Obvious

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Grounds 2, 3, and 4: Obviousness

Ground	Claims	Basis for Rejection
 1	22, 25-31	Anticipation by Zhang (Ex. 1009)
2	22, 25-31	Obviousness over Zhang
3	22, 25-31	Obviousness over Zhang and Saporito P1 (Ex. 1013) and/or Saporito P2 (Ex. 1014)
4	22, 25-31	Obviousness over Zhang, Marinus's Orphan Drug Press Release (Ex. 1011), and Marinus's Phase I Press Release (Ex. 1022)
7	22, 25-31	Lack of enablement

The slide features a light blue background with a faint, intricate pattern of white circuitry and electronic symbols, including resistors, capacitors, and various interconnecting lines. In the top left corner, the word "FISH." is displayed in a bold, black, sans-serif font, with a small blue dot following the period.

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“Unexpected Results” – Petitioner’s Clinical Trial Results Cannot Rescue PO’s Claims

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

PO's Allegedly “Unexpected Results” Are Petitioner’s Own Clinical Trial Results, Published After the’ 817 Patent Issued

Received: 15 April 2022 | Revised: 22 June 2022 | Accepted: 22 June 2022

DOI: 10.1111/epi.17143

RESEARCH ARTICLE

Epilepsia

Epilepsia

Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial

Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial

Henrikas Vaitkevicius^{1,2} | R. Eugene Ramsay³ | Christa B. Swisher⁴ |
Audi M. Hsuan⁵ | Alex Aimeri⁶ | Marcie Gastor⁷

Abstract
Objective: Patients with refractory status epilepticus (RSE) have failed treatment with benzodiazepines and 21 second-line intravenous (IV) antiepileptic medication (ASM). Guidelines recommend IV anesthetics when second-line ASMs have failed, but potential harms can outweigh the benefits. Novel treatments are needed to stop and durably control RSE without escalation to IV anesthetics. Ganaxolone is an investigational nonconvulsive anesthetic in development for RSE treatment. This study was designed to evaluate the efficacy and safety of ganaxolone in RSE and obtain a preliminary assessment of efficacy and safety.
Methods: This was an open-label, phase 2 trial conducted from February 19, 2018 to September 18, 2019, at three sites in the United States. Patients were aged ≥12 years, had convulsive or nonconvulsive SE, and failed to respond to 21 second-line IV ASM. Twenty-one patients were screened; 17 were enrolled. Patients received IV ganaxolone added to standard-of-care ASMs. Ganaxolone infusion was initiated as an IV bolus (over 3 min) with continuous infusion of decreasing infusion rates for 48-h followed by an 1-h taper. There were three treatment groups: 0.5 mg/kg bolus followed by 0.5 mg/kg/h infusion (n = 7), 0.5 mg/kg bolus followed by 0.5 mg/kg/h infusion (n = 7), and 0.5 mg/kg bolus followed by 0.5 mg/kg/h infusion (n = 7). The primary end point was the number of patients not requiring escalation to IV anesthetic treatment within 24 h of ganaxolone initiation.
Results: Most of the 17 enrolled patients (65%) had nonconvulsive SE, and had failed a median of three prior ASMs, including first-line benzodiazepine and second-line IV ASM therapy. Median time to SE cessation following ganaxolone initiation was 5 min. No patient required escalation to third-line IV anesthetics during the 24-h period following ganaxolone initiation. Two treatment-related serious adverse events (sedation) were reported. Of the three deaths, none were reported for publication.

Henrikas Vaitkevicius was affiliated with 1 of the time the trial was conducted.

Clinical Trial Registration: NCT03350035

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Ovid Exhibit 2003 - Page 1 of 11
Marius v. Ovid - FGR2023-00020

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Ex. 2003

POPR at 43-52; POR at 40-49

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

The Allegedly “Unexpected Results”

Claim(s)	Allegedly Unexpected Result from Ex. 2003	POPR, POR & Sankar Declaration
22	Lack of treatment escalation 24 h following completion of infusion (Table 2, row 3)	POR, 45; Ex. 1014, ¶¶113
	Lack of relapse in 85% of evaluable patients four weeks after completion of infusion (page 2386)	
25-31	Rapid & sustained effect observed for “High” dose cohort in clinical trial (page 2386)	POR, 45-48 and 49
	“Rapid” seizure cessation and reduction in seizure burden (page 2388)	
30	Lack of recurrence of SE after discontinuation of ganaxolone infusion (page 2388)	POR, 44; Ex. 1014, ¶¶109-112
	Rapid & sustained effect observed for “High” dose cohort in clinical trial (page 2386)	

Reply at 19

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

But Those Results Do Not Support the Non-Obviousness of PO's Broad Claims



“It is the established rule that ‘objective evidence of non-obviousness must be **commensurate in scope** with the claims which the evidence is offered to support.’”

Allergan, Inc. v. Apotex, Inc., 754 F.3d 952, 965 (Fed. Cir. 2014)
(emphasis added)

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Reply at 18-20

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DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Petitioner's Clinical Trial Required a Very Specific Dosing Regimen

2.2 | Treatment

Patients received IV ganaxolone in addition to ongoing treatment with second-line IV ASMs. Investigators were instructed to confirm that dosing of ASMs was consistent with the Internal League Against Epilepsy's (ILAE's) generally recommended loading/maintenance doses of ASMs.⁵ The formulation of ganaxolone used in this trial was solubilized by Captisol® (betadex sulfobutyl ether sodium), which had a daily exposure limit up to 50 g/day at the time the trial was conducted. As per protocol, patients who were ≥40 kg were to receive a fixed dose of ganaxolone; those <40 kg were to receive mg/kg dosing. Because no patients weighed <40 kg, ganaxolone was studied in the following three dose cohorts: 500 mg/day (low), 650 mg/day (medium), and 713 mg/day (high, the most ganaxolone that could be administered while staying within the daily Captisol® limit) (Figure 1). In all dose cohorts, ganaxolone infusion was initiated as an IV bolus (over 3 min) with continuous infusion of decreasing infusion rates for 48–96 h followed by an 18-h taper (see Table S1 for details). Additional as-needed boluses were allowed in the Medium Cohort. These infusion parameters allowed for rapid loading of ganaxolone (plasma concentration ~900 ng/ml) designed to abort SE, followed by maintenance doses aimed at sustaining seizure control (Figure 2). If, in the opinion of the investigator, the patient was deriving continuing benefit, ganaxolone infusion could have been extended for an additional 48 h (total of 96 h), followed by a taper. Once the ganaxolone infusion was completed, patients were subject to in-person 24-h, 48-h, and 72-h assessments and to additional visits at weeks 2, 3, and 4 (follow-up), which were conducted in-person or via telephone.

Which PO did Not Provide

ing within the daily Captisol® limit) (Figure 1). In all dose cohorts, ganaxolone infusion was initiated as an IV bolus (over 3 min) with continuous infusion of decreasing infusion rates for 48–96 h followed by an 18-h taper (see Table S1 for details). Additional as-needed boluses were allowed in the Medium Cohort. These infusion parameters allowed for rapid loading of ganaxolone (plasma concentration ~900 ng/ml) designed to abort SE, followed by maintenance doses aimed at sustaining seizure control (Figure 2). If, in the opinion of the investigator, the pa-

And PO's Expert Did Not Consider

Q. Did you review Table S1 in forming your opinions?

A. No, I didn't.

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Ex. 2003; Ex. 1055; Ex. 1041 at ¶ 65; Ex. 1042 at 58:7-18
Reply at 20-21

Vaitkevicius Table S1 (Ex. 1055)

Vaitkevicius et al. Supplemental Material

Supplemental Table 1. Ganaxolone dosing used in this study

Cohort	Initial Bolus ^a	Additional Boluses PRN	Day 1 Infusion Rates	Day 2 - 4 Infusion Rates	18-h Taper ^b
High (713 mg/d)	25 mg	Not allowed	80 mg/h for 2 h 40 mg/h for 6 h 18 mg/h for 16 h	29 mg/h for 24 h	25% rate decrease every 6 h
Medium (650 mg/d)	25 mg	Allowed ^c	35 mg/h for 12 h 25 mg/h for 4 h 13 mg/h for 8 h	25 mg/h for 24 h	
Low (500 mg/d)	30 mg	Not allowed	85 mg/h for 2 h 40 mg/h for 2 h 20 mg/h for 2 h 10 mg/h for 18 h	20 mg/h for 24 h	

^aInitial bolus was delivered over 3 min.

^bTaper was initiated at the end of continuous infusion (i.e., Day 2, Day 4, or Early Discontinuation for those subjects who did not progress to 3rd line IV anesthesia for SE treatment). Ganaxolone infusion was stopped without taper in subjects who progressed to 3rd line anesthesia for SE treatment.

^cAdditional as-needed boluses were allowed in the Medium Cohort in the maximum total daily dose of up to 65 mg on Day 1 and up to 114 mg on Days 2-4 to manage seizures. It was recommended that a single dose of bolus was not to exceed 25 mg.

Petitioner's Specific Dosing Regimens Gave Rise to Unexpected Results

Houlihan Declaration (Ex. 2007):

8. In our clinical investigations, we unexpectedly discovered that SE could be rapidly and persistently suppressed using less ganaxolone and for a much shorter period of time than was anticipated. We determined that administering ganaxolone as an intravenous bolus and continuous intravenous infusion to achieve and maintain a ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml for about 8 to about 12 hours resulted in rapid and persistent suppression of SE, without recurrence of SE when the rate of ganaxolone infusion was reduced and treatment was terminated (See, FIG. 15 of the patent application¹).

9. Our investigations also surprisingly revealed that targeting a transient ganaxolone plasma concentration of about 500 ng/ml to about 1000 ng/ml was not enough to result in persistent suppression of SE. We found that it is important to maintain that ganaxolone plasma concentration for about 8 to about 12 hours to achieve persistent suppression, i.e., to break SE. In fact, when the plasma concentration dropped below 500 ng/ml prior to completing 8 to 12 hours of treatment, seizures rapidly recurred. (See, FIGS. 3, 5, 7, 9 and 15 of the patent application.)

10. It was completely unexpected that providing ganaxolone at a serum concentration of about 500 ng/ml to about 1000 ng/ml for a short duration of only about 8 to about 12 hours, resulted in persistent SE suppression. In fact, it was completely contrary to c expectations.

“intravenous bolus plus continuous infusion . . .”

Pending Independent Claim (Ex. 2007):

55. (Currently Amended) A method of treating status epilepticus (SE), comprising administering to a subject in need thereof an effective amount of ganaxolone to suppress SE for a period of at least 8 hours, wherein the effective amount of ganaxolone is administered as an intravenous bolus plus continuous infusion to produce and maintain a ganaxolone plasma concentration of at least about 500 ng/ml for at least about 8 hours to about 12 hours, the amount of ganaxolone infused into said subject by said continuous infusion is decreased at least once during said about 8 hours to about 12 hours to produce and maintain a ~~while the~~ ganaxolone plasma concentration of at least about 500 ng/ml to about 1000 ng/ml for the remainder of said about 8 hours to about 12 hours ~~is maintained~~; and the total daily dose of ganaxolone administered is from about 500 mg to about 900 mg.

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Ex. 2007 at 29-32; see also Ex. 2008 at 25-28
Reply at 22-25

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But PO's Claims Do not Recite any Specific Dosing Regimen

Dr. Sankar:

Q. Okay. But in that context then there's no dosage regimen described in claim 22 or incorporated into claim 22; correct?

MS. PEHRSON: Same objection.

THE WITNESS: Yeah, as stated, no.

Q. And then claim 25 says, "The method of claim 21," again, so it's a depending from claim 21, "wherein the patient is administered about 500 milligrams to about 1,000 milligrams per day ganaxolone." Do you see that?

A. Yes.

Q. So that provides a range of daily doses; correct?

A. Correct.

BY MR. KANE:

Q. Could that be a single dose of 500 to -- 500 milligrams to 1,000 milligrams in a 24-hour period?

MS. PEHRSON: Objection. Vague.

THE WITNESS: It doesn't say that here. It says elsewhere that it could be twice a day, three times a day. That's a number of options that's been covered but not in this particular statement. It just refers to the daily dose.

BY MR. KANE:

Q. So it would cover all the options as long as they fell within that range?

MS. PEHRSON: Objection. Calls for a legal conclusion.

MR. KANE: Why don't you read back the question. (Record read.)

THE WITNESS: Yes.

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Ex. 1042 at 45-48
Reply at 25-30

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PO's Expert Confirms that the Claims Are Not Commensurate In Scope

Ex. 2003

Reductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts. Patients in the high-dose

Dr. Sankar:

BY MR. KANE:

- Q. And then it continues on to say, "Reductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts." Do you see that?
- A. Yes.
- Q. And we talked about that a couple of times, that's the function of the bolus?
- A. Yes.

Claim(s)	Allegedly Unexpected Result from Ex. 2003	POPR, POR & Sankar Declaration
22	Lack of treatment escalation 24 h following completion of infusion (Table 2, row 3) Lack of relapse in 85% of evaluable patients four weeks after completion of infusion (page 2386)	POR, 45; Ex. 1014, ¶113
25-31	Rapid & sustained effect observed for "High" dose cohort in clinical trial (page 2386) "Rapid" seizure cessation and reduction in seizure burden (page 2386) Lack of recurrence of SE after discontinuation of ganaxolone infusion (page 2388)	POR, 45-48 and 49 POR, 44; Ex. 1014, ¶¶109-112
30	Rapid & sustained effect observed for "High" dose cohort in clinical trial (page 2386)	POR, 45-48; Ex. 1014, ¶¶113-116

Ex. 2003 at 2388; Ex. 1042 at 65:2-8
Reply at 19, 25-30



PO's Expert Confirms that the Claims Are Not Commensurate In Scope

Dr. Sankar:

Q. And then it says, "Patients in the high dose cohort maintain ganaxolone plasma concentrations greater than 500 nanograms per ml for eight hours following treatment initiation and demonstrated the most durable reductions in seizure burden"; correct?

A. Yes.

Q. And that 500 -- the 500 nanogram per ml plasma concentrations is a function of the dosing regimen?

A. It's the result of the bolus but not everybody will get the same blood level. It depends also on the patient's factors pertaining to an individual patient.

Q. Well, it's a function of the bolus and then the continuous infusion afterwards?

A. Yes.

Q. Because only the high dose patients maintain that level; correct?

A. Correct.

Ex. 2003

needed (Table S1). Sustained clinical response was associated with maintaining ganaxolone plasma concentrations ≥ 500 ng/ml. Ganaxolone plasma levels ≥ 500 ng/ml were achieved only briefly during the initial bolus for patients in the medium-dose cohort, whereas those in low- and high-dose cohorts maintained such levels for 4 and 8 h, respectively. The greatest decrease in seizure burden was seen when ganaxolone concentrations were maintained at ≥ 500 ng/ml for at least 8 h.

Reductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts. Patients in the high-dose cohort maintained ganaxolone plasma concentrations ≥ 500 ng/ml for 8 h following treatment initiation and demonstrated the most durable reductions in seizure burden. Although not studied in the present trial, main-

Claim(s)	Allegedly Unexpected Result from Ex. 2003	POPR, POR & Sankar Declaration
22	Lack of treatment escalation 24 h following completion of infusion (Table 2, row 3) Lack of relapse in 85% of evaluable patients four weeks after completion of infusion (page 2386)	POR, 45; Ex. 1014, ¶113
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30	Rapid & sustained effect observed for "High" dose cohort in clinical trial (page 2386)	POR, 45-48; Ex. 1014, ¶¶113-116

Ex. 1042 at 45-48; Ex. 2003 at 2386, 2388
Reply at 25-30

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PO's Expert Confirms that the Claims Are Not Commensurate In Scope

Dr. Sankar:

Q. And then in paragraph 110 you say, "All three dose cohorts met the primary end point. No patient who received ganaxolone added to the standard of care ASMs required treatment with IV anesthetics within 24 hours of ganaxolone initiation." Do you see that?

A. Yes.
Q. If you change the dosing regimen would you necessarily expect that all patients would achieve that end point?

MS. PEHRSON: Objection. Foundation.
THE WITNESS: That's speculative.
BY MR. KANE:

Q. So for instance if you limited the bolus would you think that the patients would achieve that end point?
THE WITNESS: My suspicion is they would not have been controlled as rapidly.
BY MR. KANE:

Q. Would they have been controlled at all?
MS. PEHRSON: Objection. Calls for speculation.
THE WITNESS: Potentially.
BY MR. KANE:
Q. You don't know?
A. You don't know until you actually do that.
Q. So changing the dosing regimen could change the results?
A. Yes.

Ex. 1042 at 45-48
Reply at 25-30



Ex. 2003

TABLE 2 Onset and durability of response to ganaxolone

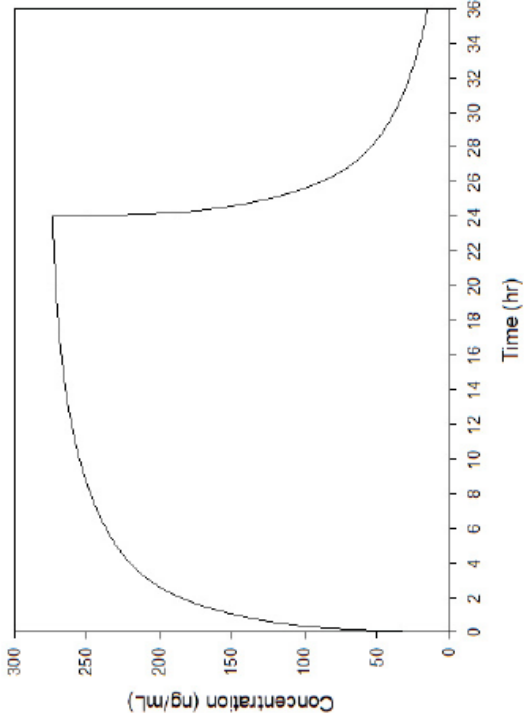
	Ganaxolone dose cohort		
	High (713 mg/day) (n = 8)	Medium (650 mg/day) (n = 4)	Low (500 mg/day) (n = 5)
No escalation to third-line IV anesthetics during 24h following infusion initiation (primary endpoint), n (%)	8 (100)	4 (100)	5 (100)
Status-free during 24 h following infusion initiation (investigator determined), n (%)	7 (88) ^a	4 (100)	5 (100)
No escalation to additional IV ASMs or to third-line IV anesthetics for status relapse during 24h following infusion completion, n (%)	8 (100)	3 (75) ^b	3 (60) ^c

Claim(s)	Allegedly Unexpected Result from Ex. 2003	POPR, POR & Sankar Declaration
22	Lack of treatment escalation 24 h following completion of infusion (Table 2, row 3) Lack of relapse in 85% of evaluable patients four weeks after completion of infusion (page 2386)	POR, 45; Ex. 1014, ¶113
25-31	Rapid & sustained effect observed for "High" dose cohort in clinical trial (page 2386) "Rapid" seizure cessation and reduction in seizure burden (page 2386) Lack of recurrence of seizures after discontinuation of ganaxolone infusion (page 2388)	POR, 45-48 and 49 POR, 44; Ex. 1014, ¶¶109-112
30	Rapid & sustained effect observed for "High" dose cohort in clinical trial (page 2386)	POR, 45-48; Ex. 1014, ¶¶113-116

Pharmacokinetic Modeling Confirms The Claims
Are Not Commensurate In Scope

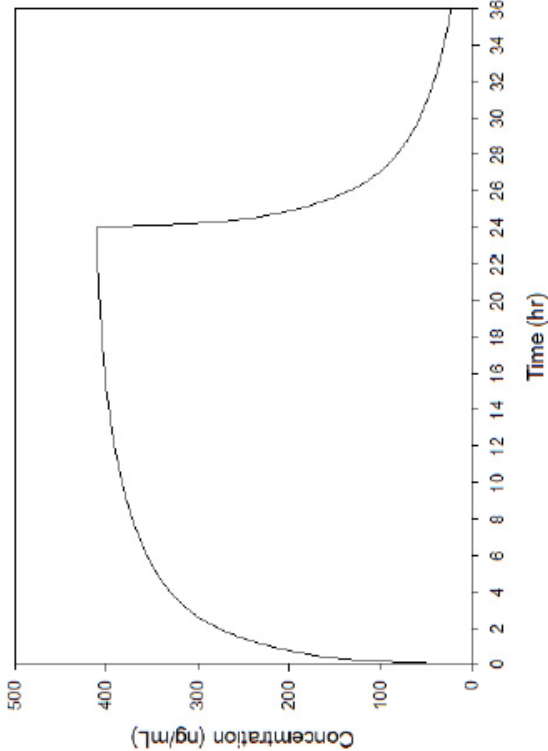
480 mg ganaxolone in One Day:

20 mg/hr IV Infusion of Ganaxolone over 24 hours



720 mg ganaxolone in One Day:

30 mg/hr IV Infusion of Ganaxolone over 24 hours



Ex. 1058 at ¶¶ 18-22.
Reply at 29-30

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PO's Claims Cannot Be Rescued from the Obviousness Conclusion by Petitioner's Clinical Trial Results



“It is the established rule that ‘objective evidence of non-obviousness must be **commensurate in scope** with the claims which the evidence is offered to support.’”

Allergan, Inc. v. Apotex, Inc., 754 F.3d 952, 965 (Fed. Cir. 2014)
(emphasis added)

Reply at 18-20

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If the Prior Art is Insufficient to Anticipate and/or Render Obvious, then the Claims Are Not Enabled

Ground 7: Enablement

G. GROUND 7: Claims 1–3, 10–17, and 19–31 Are Not Enabled

As noted above, in Section IV.B, the '817 patent specification contains very little data to support its claims related to treating SE with ganaxolone. If Ovid takes the position that the references applied to Challenged Claims 1–3, 10–17, and 19–31, above—which contain as much and, in fact, *more* data to support treating SE with ganaxolone—do not anticipate and/or render them obvious by arguing that the references are not enabling, then the claims of the '817 cannot be enabled.²⁸⁷

Petition at 74-77

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Specification Discloses No More than Prior Art

Specification just shows effects measured after 2 hours and 24-hour survival

gaboxadol). All rats are observed and scored for seizure severity for 120 min post drug administration, and any accompanying behavioral effects are also noted by an experimenter blinded to treatment conditions. At the con-

lack of efficacy, the highest dose tested is noted. Additional measures of effects, e.g., motor impairment, weight change post-SE, or survival from SE for 24 hrs are also recorded during the studies for all treatment conditions.

TABLE 2

Overall survival and protection results			
Compound (dose, mg/kg)	Protection (includes PK rats)	24-hour Survival (excludes PK rats)	
VEH (40% HPBCD)	0/13 (0%)	8/11 [#] (72%)	
ALLO (0.5 mg/kg)	0/13 (0%)	6/10 (60%)	
GBD (0.5 mg/kg)	2/13 (15%)	7/10 (70%)	
GNX (0.5 mg/kg)	0/13 (0%)	6/10 (60%)	
ALLO (2 mg/kg)	0/13 (0%)	7/10 (70%)	
GBD (2 mg/kg)	0/13 (0%)	8/10 (80%)	
GNX (2 mg/kg)	0/13 (0%)	8/10 (80%)	
ALLO (5 mg/kg)	0/13 (0%)	7/9 (72%)	
GBD (5 mg/kg)	0/13 (0%)	6/11 [#] (55%)	
GNX (5 mg/kg)	0/13 (0%)	7/10 (70%)	
ALLO (10 mg/kg)	2/13 (15%)	9/10 (90%)	
GBD (10 mg/kg)	0/13 (0%)	10/10 (100%)*	
GNX (10 mg/kg)	1/13 (7.7%)	9/10 (90%)	
ALLO (20 mg/kg)	1/13 (7.7%)	9/10 (90%)	
GBD (20 mg/kg)	0/13 (0%)	7/9 (78%)	
GNX (20 mg/kg)	4/13 (30.8%)*	9/10 (90%)	

*Significantly different from VEH, p < 0.05

[#]Spontaneous death during SE in PK group rat 110 min post -SE onset, but sample was collected.

Specification Discloses No More than Prior Art

Only data in specification is rat data

Example 3

Evaluation of the Ability of Allopregnanolone,
Ganaxolone, and Gaboxadol to Block
Benzodiazepine-Resistant Status Epilepticus

Allopregnanolone, ganaxolone, and gaboxadol are evaluated for acute anticonvulsant efficacy when administered with escalating doses at 30 min after the onset of convulsive status epilepticus, a time-point typically resistant to benzodiazepines. Results obtained with these agents are compared to those obtained from side-by-side studies with vehicle-treated animals.

Twenty-four hours prior to administration of the chemodant pilocarpine, male Sprague Dawley rats (n=10) or treatment/group, 100-125 g; Charles River Laboratories) are treated systemically with lithium chloride (127 mg/kg; intraperitoneal (i.p.)). On the next day, the rats receive pilocarpine hydrochloride (50 mg/kg; i.p.) and are monitored carefully for the presence or absence of convulsive seizure activity. Administration of pilocarpine induces

Ex. 1001 at Example 3
Petition at 74-78

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Specification Discloses No More than Prior Art

Data in specification was from
I.P. administration

administration is excluded from further study. On the study day, the ability of each of the investigational compounds (allopregnanolone (ALLO), ganaxolone (GNX), or gaboxadol (GBD)) or vehicle (VEH) (40% hydroxypropyl β -cyclodextrin) to halt convulsive status epilepticus in the Li-Pilo model of status epilepticus is evaluated with escalating doses administered i.p. 30 min after the first observed convulsive seizure. Throughout the study, the experimenter conducting the behavioral observations is blinded to treatment conditions (i.e., allopregnanolone, ganaxolone, or gaboxadol). All rats are observed and scored for seizure severity for 120 min post drug administration, and any accompanying behavioral effects are also noted by an experimenter blinded to treatment conditions. At the con-

Ex. 1001 at Example 3
Petition at 74-78

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The End

PGR2023-00020

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Petitioner's Presentation

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DEMONSTRATIVE EXHIBIT - NOT EVIDENCE