1 UNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD
3 _____
4 MARINUS PHARMACEUTICALS,)
INC.,)
5)
Petitioner,)
6)
vs.) No. PGR2023-00020
7) Patent 11,395,817
)
8 OVID THERAPEUTICS, INC.,)
)
9 Patent Owner.)
)
10 _____)
11
12
13 DEPOSITION OF RAMAN SANKAR, M.D. PH.D
14 FRIDAY, FEBRUARY 9, 2024
15 LOS ANGELES, CALIFORNIA
16
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24 REPORTED BY: JEANINE CURCIONE
25 CSR NO. 10223, RPR

1 Deposition of RAMAN SANKAR, M.D. PH.D, taken on behalf
2 of Petitioner, at 9:28 A.M., Friday, February 9, 2024
3 at 930 Hilgard Avenue, Los Angeles, California, before
4 Jeanine Curcione, C.S.R. No. 10223, RPR, pursuant to
5 notice.
6
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1 I N D E X

2

3 WITNESS EXAMINATION PAGE

4 RAMAN SANKAR, M.D. PH.D

5 BY MR. KANE 4

6

7 E X H I B I T S

8 NO. PAGE DESCRIPTION

9 Exhibit 1001 25 Patent Number 817 B2

10 Exhibit 1009 88 International Publication Patent
Number WO 2016/12710 A1

11 Exhibit 1011 85 Marinus Press Release re FDA Orphan
12 Drug Designation for Ganaxolone IV

13 Exhibit 1013 94 Marinus Article on Ganaxolone IV

14 Exhibit 1050 89 Veterinarian Publication - "Status
Epilepticus and Cluster Seizures"

15 Exhibit 1051 90 Article from Journal of Veterinary
16 Internal Medicine re Management of
Epilepticus and Cluster Seizures in
17 Dogs and Cats

18 Exhibit 2003 43 Article from Epilepsia re Ganaxolone
for Refractory Status Epilepticus

19 Exhibit 2008 69 Preliminary Amendment

20 Exhibit 2014 13 Declaration of Raman Sankar, M.D.
21 PH.D

22 ******

23

24

25

LOS ANGELES, CALIFORNIA;
FRIDAY, FEBRUARY 9, 2024, 9:28 A.M.

RAMAN SANKAR, M.D. PH.D,
having been duly affirmed, was
examined and testified as follows:

EXAMINATION

BY MR. KANE:
Q. Good morning.
A. Good morning.
Q. Sorry for the delay. Can you please state your full name and address for the record?
A. Raman Sankar. Address at work or home?
Q. Home address will be fine.
A. 1745 Selby Avenue, S-e-l-b-y, Avenue, number 8, Los Angeles, California 90024.
Q. Dr. Sankar, have you ever been deposed before?
A. Yes.
Q. How many times?
A. Probably less than half a dozen times over the years.
Q. Did any of those depositions relate to patent?

A. No.
Q. What kind of subject matter?
A. They were mostly about clinical practice related one, things for the hospital was involved in some litigation.
Q. Have any of those depositions related in any way to Ganaxolone?
A. No.
Q. So I'm sure your lawyer has gone over with you the ground rules today but I'm going to ask you a series of questions. We have a court reporter who's taking down what we're saying so I will try to make sure that you are finished answering before I speak and if you can wait and let me finish my question before you speak that helps her out. Do you understand?
A. Yes.
Q. You need to -- because she is taking it down we need to have verbal yeses, nos, not shaking of the head or huh-uh or uh-huh, those kind of things.
I'm going to be asking you questions. If you don't understand my question or you want me to try to clarify it, please let me know. If you answer the question I'm going to assume that it was clear and you understood it. Is that okay?
A. Yes.

1 Q. Your attorney may make some objections today
2 but generally you will be still answering the
3 questions. Do you understand that?
4 A. Yes.
5 Q. Is there any reason that you can't give
6 complete and accurate testimony today?
7 A. No.
8 Q. Could you briefly describe your education
9 and training?
10 A. Yes. I did my undergraduate education at
11 the University of Bombay and then I subsequently
12 obtained a Ph.D. from the University of Washington in
13 Seattle in pharmaceutical sciences with emphasis on
14 drug design of medicine and chemistry. And then I had
15 a year of postdoctoral fellowship followed by teaching
16 pharmaceutical chemistry for seven years after which I
17 entered Tulane medical school in 1982 and graduated
18 with my M.D. in 1986. After that I came to
19 Los Angeles, trained in pediatrics for two years at
20 Children's Hospital of Los Angeles. Then from '88 to
21 '91 I was at UCLA as a resident and fellow in pediatric
22 neurology and I joined the faculty in 1991 so this is
23 my 33rd year on the faculty.
24 Q. And what do you consider or how would you
25 describe your area of expertise?

1 A. My area of expertise is substantially
2 epilepsy in a broad clinical sense. On the basic
3 science side I live a dual life of scientist and
4 clinician, and my scientific side has been involved in
5 physiology pharmacology of medications used to treat
6 seizures.
7 Q. Do you teach courses?
8 A. Yes.
9 Q. What courses are you currently teaching?
10 A. I teach substantially not the typical
11 undergraduate medical education courses because the
12 field of pediatric epilepsy is a pretty narrow and
13 specialized field. A large number of people don't know
14 we exist. So the ones I teach tend to be people who
15 are doing either a neurology residency or a pediatric
16 residency when they don't take to my service
17 clinically. Or more advanced trainees who have
18 finished neurology but are specializing in epilepsy,
19 pediatric neurologist specializing in epilepsy.
20 Primary care people don't get that far involved. But
21 when I'm on clinical service they rotate with me so
22 they get a basic knowledge of it.
23 Q. Do you treat patients?
24 A. Yes. Quite regularly.
25 Q. What types of patients do you treat?

1 A. For the most part patients with seizure
2 disorders but I do treat some people with migraines and
3 developmental disorders but what I'm known for
4 worldwide is epilepsy.
5 Q. Is it primarily adult or pediatric?
6 A. It's primary pediatric but as it happens
7 throughout this country transitional complex pediatrics
8 patients is very challenging, so right now probably a
9 third of my patients are adults. They used to be young
10 once and have grown up and they have never sort of
11 moved on. So we tend to have that type of a practice.
12 Q. Have you treated patients with status
13 epilepticus?
14 A. Yes.
15 Q. And can we refer to that as SE today?
16 A. Yes, we do.
17 Q. So what's your experience in treating
18 patients with SE?
19 A. Can you clarify exactly what you mean?
20 Q. You said you've treated patients with SE;
21 correct?
22 A. Yes.
23 Q. And can you give me some idea of the breadth
24 of that experience?
25 A. Yes. Sometimes people meet the definition

1 of SE and are relatively not so challenging to control,
2 and a lot of times our challenge in taking care of them
3 has a lot to do with what caused the SE. Sometimes
4 people come up with SE for reasons such as they missed
5 medication. We live in a situation where pharmacies
6 won't fill them thanks to insurances until you have the
7 last pill, and sometimes you'll go Friday to your store
8 and they may say we don't have it. You have to wait
9 until Tuesday for us to get it.
10 So there are these practical issues and
11 other times it's just lack of compliance as we call it.
12 Those are the easier ones to manage usually because we
13 can control their seizures and pack up their
14 medications. Other times it may be an acute and severe
15 illness, such as severe trauma, stroke, particularly
16 infectious reasons like meningitis or brain cancer.
17 Those sometimes can be extremely challenging, and some
18 of the worst cases are autoimmune encephalitis.
19 Q. Have you ever administered ganaxolone to a
20 patient?
21 A. I have not.
22 Q. Have you been involved in drug development?
23 A. Yes.
24 Q. What's your experience been in the drug
25 development process?

1 A. Well, what I have seen over and over is that
2 a very large number of compounds often seem promising
3 in the early stage and then less than 1 percent of them
4 actually make it to the clinic.
5 Q. Have you ever been involved with designing a
6 clinical trial?
7 A. I have been part of a group of people as an
8 advisory board to work with pharma to design a clinic
9 trial.
10 Q. Have you ever done any work for Ovid?
11 A. I have not worked for Ovid, no.
12 Q. How about for Marinus?
13 A. I have not worked for Marinus.
14 Q. In the advisory board role what did you
15 contribute typically?
16 A. Typically we look at the study design,
17 patient selection for instance. Patient exclusion. A
18 lot of the big picture things are kind of set because
19 there's a number of things you have to do in order for
20 it to be acceptable by the FDA. So usually the
21 pharmaceutical companies negotiate terms of this
22 clinical trial. There's no sense in spending millions
23 of dollars if the FDA is not going to accept the study
24 design.
25 So in the world of seizures there's a lot of

1 standard parameters for seizure drugs typically, you
2 know, how they get randomized and how long they go on,
3 whether there's an open label at the end of it or not,
4 most of those things are etched in stone.
5 Q. So is your role primarily in terms of
6 patient selection?
7 A. We talk about all of them including the
8 science whether it fits.
9 Q. Do you have expertise in pharmacokinetics or
10 pharmacodynamics?
11 A. Yes, I do.
12 Q. And what's your experience in that realm?
13 A. In that realm the pharmacokinetic aspects
14 determine how the medication is going to be dosed. In
15 modern times people don't like multiple doses.
16 People's adherence is best if they can take it just
17 once or twice a day. And then the dosing also depends
18 on the rate of elimination from the body and sometimes
19 pharmacokinetic aspects may be confounded by drug
20 interactions of how they play with other medications a
21 patient is on, so all those come into focus.
22 Q. So in those roles on the advisory board have
23 you ever been involved in a drug that has come to
24 market?
25 A. Yes.

1 Q. Which drugs?
2 A. I've been involved with the medications,
3 many of them that were developed by UCB such as
4 levetiracetam, lacosamide, some of those. I've been
5 involved with advisory boards for oxcarbazepine in the
6 old days, zonisamide. A good number of medications
7 actually.
8 Q. And what are those medications used for?
9 A. Seizures.
10 Q. Any of them used for SE?
11 A. Well, the subset of them generally
12 medications used for SE need to be available as an
13 injectable version. Occasionally in dire straights
14 when patients are not responding they may bring on
15 others that have promise but are not available
16 intravenously by nasogastric tube or something. We
17 have been done that occasionally but those are not
18 specifically labeled for SE.
19 Q. So some of the drugs you use to treat SE are
20 off label?
21 A. Yeah. They're not off label for treating
22 seizure disorders. Very few things come labeled
23 specifically for SE. The drugs used for SE typically
24 are used for seizure disorders.
25 Q. Are there any drugs that are labeled for SE

1 that you're aware of?
2 A. Specifically at the moment I can't think of
3 any that we used for SE that's not already used for
4 seizure disorders. Going back to nearly a century,
5 starting with phenytoin or something.
6 Q. Dr. Sankar, I've handed you what's been
7 marked as Exhibit 2014, it's titled "Declaration of
8 Raman Sankar, M.D." Do you see that?
9 (Exhibit 2014 was marked for identification
10 by the Reporter.)
11 THE WITNESS: Uh-huh.
12 BY MR. KANE:
13 Q. Is this the declaration that you provided in
14 connection with this proceeding?
15 A. Yes.
16 Q. When were you retained to work on this
17 matter?
18 A. Sometime in August of '23.
19 Q. And how were you contacted?
20 A. I was contacted by one of the medical
21 officers with Ovid who has known me for a long time
22 because prior to Ovid he was a medical officer at Kazi,
23 another pharmaceutical company and he has worked with
24 me on advisory boards and he knew particularly my basic
25 science background and he asked me if I could get

1 involved with these people.
2 Q. And what's that person's name?
3 A. Manoj Malhotra.
4 Q. Do you want to spell that?
5 A. First name is M-a-n-o-j. Last name is
6 M-a-l-h-o-t-r-a.
7 Q. And when he contacted you what did he
8 describe the matter as involving?
9 A. He did not tell me specifically what the
10 issues were. He merely said there was some IP issue
11 going on and he thought I may be able to provide
12 insightful help with that matter and if I would then
13 agree to do that he would put me in connection with
14 people. And then I worked with the counsel.
15 Q. And what was the process that you utilized
16 to generate this report?
17 MS. PEHRSON: Dr. Sankar, I just advise you not
18 to disclose any substance of communications with your
19 counsel.
20 THE WITNESS: I used a number of materials
21 including published literature as well as the patents
22 and the rebuttals.
23 BY MR. KANE:
24 Q. Did counsel provide all the materials to
25 you?

1 A. Yes.
2 Q. Did you do any independent searching
3 yourself?
4 A. I did. I used PubMed to look up a few
5 things.
6 Q. And did you find anything that you
7 incorporated into your report?
8 A. Many of them were already part of this
9 dossier.
10 Q. Can you think of any that weren't?
11 A. At the moment I can't.
12 Q. If we look at page 5 -- it's a little
13 confusing here.
14 A. Page 5 of 68?
15 Q. Let's look at page 11 of 68. Sorry.
16 There's two page numbers.
17 A. There we go. Yeah.
18 Q. All right. You see there Roman IV is
19 "Background of Technology"?
20 A. Uh-huh.
21 Q. And then it starts talking about SE.
22 A. Yeah.
23 Q. And paragraph 14 you say that SE is
24 considered to be a life threatening condition. It is
25 associated with high mortality?

1 A. Yes.
2 Q. Can you explain or expound on that?
3 MS. PEHRSON: Objection. Vague.
4 THE WITNESS: Okay. The SE carries significant
5 mortality because during this onslaught of brain
6 discharges it challenges the entire body because the
7 brain normally controls all our organs. Many patients
8 tend to -- the ones that typically die frequently die
9 from complexities of the very aggressive treatment.
10 Some of the medications particularly if they go down to
11 the level of deep anesthesia, those medications often
12 challenge the heart so usually the blood pressure
13 begins to drop. And when you try to treat that
14 condition it really -- you're stimulating the heart to
15 work harder which is hard to do because the medication
16 is treating SE are often interfering with the energy
17 metabolism of let's say the heart. So you find
18 yourself really whipping the heart but it really cannot
19 keep up with it and people often succumb to that.
20 There can be circulatory failure that causes death.
21 Q. You say here in that sentence you continue
22 on to say it's often associated with high mortality if
23 not treated immediately.
24 A. Uh-huh.
25 Q. And it could result in brain damage or

1 cognitive impairment or death; right?
2 A. Yes.
3 Q. So what is the urgency associated with SE?
4 MS. PEHRSON: Objection. Vague.
5 THE WITNESS: The most straightforward answer
6 for the urgency is as seizures continue to occur your
7 best chance to contain them is very early. The longer
8 they go on there are neurologic cellular physiology
9 causes a drop in receptors that you are approaching
10 with your medication. As you lose the receptors you're
11 not able to effectively stop.
12 So seizures can become the term use is self
13 sustaining and they become more and more difficult to
14 treat and when they become very difficult to treat with
15 typical seizure meds the next step usually is
16 escalation to anesthesia. That of course brings on
17 much more risk.
18 Q. And so in treating a patient with SE what
19 would be the normal course of therapy and escalation?
20 A. Most commonly if a patient is found in SE at
21 the emergency department the very first line of
22 medications usually are benzodiazepine. It may be
23 Valium but much more commonly lorazepam, also called
24 Ativan. That's usually the first line people get. And
25 usually if that doesn't control it, if it's progressing

1 they'll get, quote, loaded intravenously, and at the
2 current state-of-the-art it's three or four medications
3 that are very commonly used that include phenytoin,
4 which is a very old drug, more than a century old.
5 Levetiracetam which is a much more modern drug or
6 valproate acid.
7 Those three have been published as fairly
8 equivalent, so that's what we call the second line. If
9 it goes past second line usually the patient needs to
10 be in an ICU setting or in a competent emergency
11 department because as you escalate therapy you're
12 reaching a stage where the patient cannot breathe.
13 They can't control their airway. So you need to be
14 prepared to intubate. And this is why usually when
15 status is not contained in the emergency department
16 you'll end up in the ICU setting.
17 Q. So the first line is the Valium or the
18 Ativan, is that administered orally?
19 A. No. Intravenously.
20 Q. And then you said that -- and I was unclear
21 when you said they would then be loaded intravenously?
22 A. Yeah, they would get a bolus administration
23 of levetiracetam. Valproate or phenytoin are not
24 immediately given as a bolus over one minute. Usually
25 dripped over 15, 20 minutes.

1 Q. How long after the Valium and Ativan are
2 dosed would the physician typically wait for going to
3 the second line therapy?
4 A. Well, at the end of the second line therapy
5 which is let's say they're loaded with levetiracetam or
6 Keppra, if they're still seizing it's time to alert ICU
7 and be prepared to move to a third stage. Sometime
8 people may try another round of benzodiazepine but more
9 than likely they want to be prepared to initiate some
10 form of a drip benzodiazepine such as midazolam or a
11 barbiturate type of anesthesia. So things are getting
12 serious at that point.
13 Q. I guess I'm just trying to understand the
14 timing. Is it a matter of minutes or --
15 A. All of this could unfold during the first
16 hour. It's just the nature of how things function, you
17 have to get a line in before you can administer the IV
18 medication. You have to start fluid support.
19 Q. And as you stated here the treatment needs
20 to be immediate?
21 A. Prompt, as fast as you can. Yeah.
22 Q. And is that in order to limit the potential
23 brain damage?
24 MS. PEHRSON: Objection. Vague. Foundation.
25 THE WITNESS: Brain damage usually occurs from

1 prolonged seizures. If you're looking at in the space
2 of let's say ten minutes, it's more like between ten
3 minutes and one hour there's already a big change in
4 response to benzodiazepine, like Ativan or Valium
5 because you're losing surface receptors on the neurons.
6 Because as part of the ongoing seizure activity, they
7 are getting internalized. It's called receptor
8 trafficking.
9 At the same time a different subtype of
10 receptors called glutamate receptors are being
11 mobilized to the surface. So basically the brain --
12 the system is fighting you. It's making it more
13 excitable and not giving you the opportunity to treat
14 the longer you go. This is why time is of the essence.
15 We often say time is brain.
16 Q. Are the receptors that are diminishing the
17 GABA related receptors?
18 A. Yes, they are.
19 Q. And in paragraph 15 you say, "SE does not
20 fall neatly within the category of seizure disorders.
21 It's a neurological emergency that has limited and
22 drastic options." Do you see that?
23 A. Yeah.
24 Q. And why do you say it's a neurological
25 emergency?

1 A. It's a neurologic emergency because if you
2 don't treat it very, very promptly the patient is going
3 to degrade rapidly and may die.
4 Q. And then you say it has limited and drastic
5 options. What do you mean by drastic options?
6 A. Drastic options being once you fail second
7 line therapy you're already thinking anesthesia.
8 Q. And anesthesia is a drastic option?
9 A. It certainly is, especially because in this
10 setting, it's not like you're having an operative
11 procedure. You're not starting with a healthy brain
12 and just sedating it. You're taking a brain that is
13 out of control and this person is going to be on
14 anesthesia as the first step typically overnight.
15 Q. So they would typically be on the anesthesia
16 for more than 24 hours?
17 A. Very commonly they're reevaluated overnight
18 and during this time they're on continuous EEG
19 monitoring. Electroencephalographic monitoring.
20 Q. And how long would the patients typically be
21 on anesthesia?
22 A. The procedure is if you put somebody under
23 that condition overnight you'll come back the next
24 morning and try to lower the anesthetic drip and if the
25 EEG remains suppressed -- as it gradually comes out if

1 you see seizure like patterns, you have to go back and
2 crank up the anesthesia again. And then worst case
3 scenarios I've had patients in SE that were in the ICU
4 for three, four months.
5 Q. Under anesthesia the entire time?
6 A. Yes. They undergo significant brain
7 atrophy -- they're not the same -- if they survive.
8 The mortality is pretty high too.
9 Q. You say in paragraph 16 that "The patients
10 face dire outcomes with mortality as high as
11 35 percent."
12 A. Yes.
13 Q. Is that consistent with your experience?
14 A. Yes.
15 Q. And then nearly half of surviving patients
16 have neurological deficits?
17 A. Yes. Typically that mortality rate has been
18 shown in adults as well as children, but this is the
19 fraction that enters what we call refractory status
20 that fail to respond to early therapy.
21 Q. How do you define refractory status?
22 A. Where you've gone through two lines and
23 start anesthesia the next day and they're still
24 seizing. They're not able to control it other than
25 completely suppress the brain, and that's when these

1 probabilities increase the longer you have to maintain
2 them like that.
3 Q. In paragraph 18 you say that "Petitioner
4 Marinus has employed Ovid's innovative epilepsy
5 treatment and research as a foundation for its own
6 development of ganaxolone products."
7 A. Uh-huh.
8 Q. What do you understand about Marinus's work
9 in developing ganaxolone products?
10 MS. PEHRSON: Objection. Vague.
11 THE WITNESS: Well, ganaxolone has a very long
12 history. It really goes back to 30-plus years. It's
13 kind of a surprising medication that has survived a
14 remarkable number of clinical trial failures in regular
15 epilepsy in the old days and then migraine, a number of
16 things. The company that initially made it went out of
17 business, so eventually Marinus's contribution has been
18 to start leveraging some new science that we have
19 learned about receptors and internalization which we
20 talked about.
21 We have learned more recently that there are two
22 subtypes of these receptors. There are one that are in
23 the synapse where nerves communicate with each other,
24 and then there are also extra synaptic receptors where
25 they don't seem to be internalized and may be a really

1 interesting option when ongoing seizure is diminishing
2 the synaptic receptors.
3 So that discovery came as we began to understand
4 GABA receptors better. And we also learned that
5 neurosteroids, including things that are naturally in
6 the body like progesterone derivatives activate those,
7 and that discovery that ganaxolone can act there made
8 it as a potential option for treatment of SE. And this
9 approach of targeting a different subtype of GABA
10 receptors was published by Matthew During that is there
11 in the original patent that was issued to Ovid.
12 Matthew showed that ganaxolone as well as
13 gaboxadol could be used for refractory status in
14 animals, status that failed to respond to diazepam
15 because the receptors are gone that you could leverage
16 these other receptors. So that's the finding that
17 probably inspired Marinus to take it and start doing
18 some clinical experimentation.
19 Q. Do you know when Marinus started working
20 with ganaxolone?
21 A. I don't know the exact year when they
22 started it.
23 Q. Do you know when Marinus started using
24 ganaxolone for, or working with ganaxolone for SE?
25 A. I can't name you the exact year without

1 looking at the literature references.
2 Q. Do you think it was before or after
3 Mr. During's publication?
4 A. The human studies were all after.
5 Q. How about the animal studies?
6 A. The animal studies existed in parallel.
7 There were some animal studies.
8 Q. Before or after Mr. During's work?
9 A. They were probably contemporaneous.
10 Q. Do you know if Ovid has ever done a human
11 study?
12 MS. PEHRSON: Objection --
13 BY MR. KANE:
14 Q. Do you know if Ovid has ever done a human
15 study on SE for -- with ganaxolone?
16 A. I have seen reports of human findings, yes.
17 Not Ovid, Marinus.
18 Q. And my question was has Ovid done any human
19 studies to your knowledge?
20 A. No.
21 Q. I'm going to hand you what's been marked as
22 Exhibit 1001 which is the US patent 11395817.
23 (Exhibit 1001 was marked for identification
24 by the Reporter.)
25 ///

BY MR. KANE:
Q. Have you seen this patent before?
A. Yes, I have.
Q. And this was -- you reviewed this as part of your work on this matter?
A. Correct.
Q. And is this the publication you were referring to by Mr. During?
A. Yeah. Some of these data.
Q. But when you said that he had disclosed this information with respect to the receptors is this the disclosure that you were referring to?
A. Yeah, you can see here allo, GNX or GBX. All of them are targeting this extra synaptic.
Q. My question though is there are any other publications that you were thinking of or is it this document?
A. This is one of the earliest approaches.
Q. Are there any others that you're aware?
A. Subsequently there have been many.
Q. Before this?
A. Before this I don't know.
Q. And if we look at column 35, so I think it's page 25 of the document, you see that's example 3 there?

1 A. Yeah.
2 Q. And that's a study that was done on rats
3 using the rat pilocarpine model; correct?
4 A. I'm very familiar with that model. I've
5 used it myself.
6 Q. And what is your familiarity with that
7 model?
8 A. It's one of the common models that we use in
9 the laboratory under controlled conditions to create
10 temporal lobe epilepsy which is a huge epileptic
11 problem and this is one of the models we use to create
12 it. And in rats as well there's a lot of mortality.
13 Those that survive develop temporal lobe epilepsy from
14 the brain injury.
15 Q. Can that model be used to study SE?
16 A. Yes, it has been used to study SE?
17 Q. And is that different than temporal lobe
18 epilepsy?
19 A. Temporal lobe epilepsy is a consequence in
20 survivors. But that's an epileptic condition where
21 seizures may be difficult to treat but it's not a
22 medical emergency. But many of those patients are
23 candidates for surgery sometimes and other times
24 they're treated with medications or neurostimulation.
25 Q. Is the rat pilocarpine model designed to

1 cause SE in the rats?
2 MS. PEHRSON: Objection. Vague. Foundation.
3 THE WITNESS: Well, injection of pilocarpine in
4 rats primed with lithium it just lowers the dose of
5 pilocarpine you need, it produces reliably status
6 epilepticus in rats as well as mice.
7 BY MR. KANE:
8 Q. And then this temporal lobe epilepsy is
9 something that may develop in the survivors of that
10 treatment?
11 A. Yes, consistently.
12 Q. So have you ever used a rat pilocarpine
13 model to study SE?
14 A. Yes.
15 Q. And what was your experience in that?
16 A. Well, I was the first one to publish that
17 the brain injury from this form of status was very
18 specific to stages of development. In one of my most
19 cited papers I published the difference between
20 two-week-old rat, three-week-old rat, four-week-old rat
21 and an adult rat showing very characteristic injury
22 patterns and the likelihood of developing temporal lobe
23 epilepsy. That goes back to a paper in 1998.
24 Q. And you were not, if I understand correctly,
25 not studying treatments for SE in that study; correct?

A. Not at that time. But at later time I have published some potential treatments.

Q. And what kind of treatments have you published on?

A. I published a paper showing the role of inflammation in progressive damage from SE and I showed -- I published a paper in the Journal of Neuroinflammation that we tried a number of sort of anti-inflammatory cocktails to minimize the injury and development of spontaneous seizures that will result in temporal lobe epilepsy, a person's temporal lobe epilepsy. So we have that type of treatment-oriented paper.

Q. In what role does inflammation play in that condition?

MS. PEHRSON: Objection. Vague. Foundation.

THE WITNESS: Inflammation and epilepsy and seizures are tied in a very circular path because inflammatory conditions like encephalitis give us some of the most challenging types of SE to treat. But even when you don't have an autoimmune or an infectious cause, prolonged seizures themselves produce inflammatory mediators. That's also extremely well studied. There's a large body of literature on that.

///

1 BY MR. KANE:
2 Q. And how does the inflammation affect the
3 prognosis of the patient?
4 A. Well, inflammation often accompanies
5 infection and prolonged status itself, SE produces some
6 inflammation and it can definitely be very adverse. It
7 makes, like I said it's a circular thing. Seizure
8 produces inflammation but inflammation makes seizures
9 hard to stop. Inflammation sort of primes the seizures
10 further. It's a circular pathway.
11 Q. So in your declaration starting at paragraph
12 25 on page 16 of 68?
13 A. Page --
14 Q. 16 of 68.
15 A. Yes.
16 Q. You refer -- you describe example 3. Do you
17 see that?
18 A. Yeah.
19 Q. And you state that toward the bottom of page
20 16, "Blinded behavioral observations were performed for
21 two hours after compound administration and the results
22 obtained with these compounds were compared to those
23 obtained from vehicle treated controlled rats." Do you
24 see that?
25 A. Yes.

1 Q. What are blinded behavioral observations?
2 A. What they mean by blinded is the observer in
3 the laboratory is not really aware of which animal
4 received vehicle versus which one may have received
5 either allopregnanolone or gaboxadol or ganaxolone.
6 Q. And what are the behavioral observations
7 that the researcher is looking at?
8 A. They can look at actual seizures.
9 Q. Anything else?
10 A. Mostly in this condition that's what you're
11 looking at, behavioral seizures, and you also try to
12 correlate with the EEG.
13 Q. And then you state as shown in Table 2 in
14 Figures 3 and 4, "Administration of 20 milligrams per
15 kilogram ganaxolone but not that of allopregnanolone
16 and gaboxadol was effective to induce significant
17 protection against SE characterized by no observation
18 pf further convulsive seizures after ten minutes of
19 drug administration," and you cite to Tables 2, Figures
20 3 and 4. Do you see that?
21 A. Uh-huh.
22 Q. So could you point out the information in
23 Table 2 that you're relying upon there?
24 A. That would be --
25 Q. It's column 36 of the patent. Page 25.

A. Uh-huh.
Q. So what in Table 2 shows you that there were no observation of convulsive seizures after ten minutes of drug administration?
A. The Table 2 is talking about mainly survival.
Q. Okay. And what is --
A. The middle column, protection, that 0 over 13, et cetera, that refers to whether there was active seizures going on or not. Zero means, you know, all of them were still seizing but the GBD which is gaboxadol 2013 and so on.
Q. And what is the other column, the 24-hour survival referring to?
A. How many of them. As I indicated earlier a lot of animals die after this pilocarpine status. In my lab we often lost up to 40 percent of them to mortality so this is just survival.
Q. And what is the importance of reporting the survival data in Table 2?
A. The survival data is very much in favor of ganaxolone 20-milligram per kilogram.
Q. And why do you say that?
A. Nine out of 10 survived. And if you look at ganaxolone at 10 that was very similar. But if you go

1 to 5 it was a little bit less. And if you go to 2 it
2 was less and so on.
3 Q. So what do you understand from that data?
4 A. That ganaxolone in the right dose can
5 substantially salvage these animals.
6 Q. And what do you mean by salvage?
7 A. That they survive overnight which may partly
8 be because we were able to gain control of their
9 seizures even though they were resistant to diazepam.
10 Q. And so the 24-hour survival rate is some
11 indication of being able to gain control of the seizure
12 activity?
13 A. Well, it's in addition to. You would know
14 that control of seizure activity from the EEG and
15 behavioral observation.
16 Q. Right. But if you look at for instance even
17 with the ganaxolone 20 if I'm understanding this
18 correctly it says 4 out of 13 obtain protection as
19 defined here; correct?
20 A. Uh-huh.
21 Q. But then 9 out of 10 survived?
22 A. Survived, yeah.
23 Q. So even those that didn't have protection it
24 increased the survival rate?
25 A. Survival.

1 Q. And why is that true?
2 A. It often may have made the seizures milder
3 potentially.
4 Q. And I guess in this case the protection was
5 evaluated after ten minutes; correct?
6 A. Yeah.
7 Q. Could the seizures have ceased after that
8 ten-minute window?
9 MS. PEHRSON: Objection. Vague. Foundation.
10 THE WITNESS: What I know -- I cannot speak for
11 their lab. In our lab we find often they go in and
12 out. It's not entirely continuous. We find sometimes
13 we can treat them successfully but half an hour later
14 they're back seizing again. It's a challenging
15 situation.
16 BY MR. KANE:
17 Q. Do they ever in that sort of circumstance
18 stop seizing again later then, let's say an hour later?
19 So going in and out?
20 A. They do but they pick up again. That's the
21 problem.
22 Q. What do you mean, pick up again?
23 A. Seizures start again.
24 Q. But my question is do you ever have
25 observations where the seizures stop for a period of

1 time, they start again and then stop again, start
2 again, sort of intermittent?
3 A. Yeah, that's not uncommon.
4 Q. Is there a benefit just to reducing the
5 total amount of seizures that the animal is
6 experiencing?
7 MS. PEHRSON: Objection. Vague. Foundation.
8 THE WITNESS: Well, the goal is to completely
9 stop the seizures, but it may improve the survival to
10 reduce the seizures.
11 BY MR. KANE:
12 Q. Reduce the number of seizures?
13 A. Yeah.
14 Q. How about the intensity of the seizures?
15 A. That too.
16 Q. Either of those can increase survival?
17 A. Yeah.
18 Q. And so is the survival a parameter that is
19 typically reported in these kind of studies?
20 MS. PEHRSON: Objection. Foundation.
21 THE WITNESS: In most of these studies they
22 are -- the bulk of the papers involving lithium
23 pilocarpine seizures are not so much on treatment of
24 status as much as using it as a tool to create temporal
25 lobe epilepsy, so they often would report the

1 mortality. They're trying to get them to survive so
2 you can actually see the development of epilepsy.
3 So a lot of the scientific interest is what can
4 we do with the cascade of biological events that go
5 from here to permanent epileptic condition and can be
6 intervened medically. And people commonly say at the
7 moment we don't really have a specific treatment to
8 prevent the consequence of epilepsy. We only have
9 medications that treat epileptic seizures.
10 BY MR. KANE:
11 Q. Starting at a column -- or column 36,
12 line 39 I guess above the table there, Table 2, the
13 sentence says, "Additional measures of effects, e.g.
14 motor impairment, weight change post SE or survival
15 from SE for 24 hours are also recorded during studies
16 for all treatment conditions." Do you see that?
17 A. Yeah.
18 Q. Why are they reporting these other effects
19 such as motor impairment?
20 MS. PEHRSON: Objection. Foundation.
21 THE WITNESS: I think these are routine
22 observations that you do to report. Because here it's
23 very difficult to discern motor impairment from
24 medication versus the seizures themselves. All the
25 medications we use in managing SE will produce motor

1 impairment on their own. They're just documenting what
2 they see.
3 BY MR. KANE:
4 Q. How about weight change?
5 A. Weight change?
6 Q. Yeah. Weight change. If you look there it
7 says "motor impairment" and then it says "weight change
8 post SE."
9 A. Weight change, you will see it over 24 hours
10 because they're not eating. They're not drinking
11 unless you hydrate them NG, nasogastric.
12 Q. And then we talked about this a bit already
13 but it says "or survival from SE." And why are they
14 reporting survival?
15 MS. PEHRSON: Objection. Foundation.
16 THE WITNESS: It's pretty common that we want to
17 know how many rats survived. We know lithium
18 pilocarpine has significant mortality associated with
19 it. So in a study pertaining to treatment, if you
20 increase survival that will be a beneficial outcome in
21 treatment.
22 BY MR. KANE:
23 Q. You also in paragraph 25 of your declaration
24 refer to Figures 3 and 4 of the patent which are on
25 page 5.

A. Yes.
Q. So starting with Figure 3 what do you understand that to be disclosing?
A. This is the dropping of a percentage protected with these three interventions including the dose, and what you find is allo is shown at a dose that in this case what looks like around 8-milligram per kilogram or so. Ganaxolone is shown in the parallel lines that was used in the neighborhood of maybe 12, and gaboxadol is the checkered one that was shown in three different -- actually only one dose, .5 milligram per kilogram.
Q. And --
A. And the 24-hour survival below on Figure 4 you can see that all three of them the survival goes up with increasing dose. But it kind of backouts around -- it's not a huge difference -- between 10 and 20 milligrams.
Q. In paragraph 26 then you say, "Both the ten milligram per kilogram and 20 milligram per kilogram of ganaxolone treatment also promoted 24-hour survival of the experimental animals although the effects were not statistically significant." Do you see that?
A. Huh-huh.
Q. Then you continue to say as shown in Figure

1 5, "All doses of ganaxolone examined, except the lowest
2 dose, reduced the number of observed seizures after
3 treatment"; correct?
4 A. Correct.
5 Q. And so that's Figure 5 on page 6. What is
6 the importance of showing the reduced number of
7 observed seizures?
8 MS. PEHRSON: Objection. Vague. Foundation.
9 THE WITNESS: Can you rephrase the question?
10 BY MR. KANE:
11 Q. Yeah, I'm curious. You made this
12 observation with respect to Figure 5. Why did you
13 include that in your declaration?
14 A. Just to state the efficacy of ganaxolone.
15 Q. And how does that relate to the efficacy of
16 ganaxolone?
17 MS. PEHRSON: Objection. Vague. Foundation.
18 THE WITNESS: That the percentage of observed
19 seizures is down.
20 BY MR. KANE:
21 Q. And is that a beneficial outcome?
22 A. Yeah.
23 Q. If you then look at example 4 of the patent
24 which is on page 26?
25 A. Uh-huh.

1 Q. And you see that's a prospective study?
2 A. Huh.
3 Q. So that's a study to be conducted in the
4 future; correct?
5 A. Yeah.
6 Q. So there's no results reported there; right?
7 A. No. It's a study design basically.
8 MR. KANE: We've been going about an hour.
9 Let's take a short break.
10 (Recess taken.)
11 BY MR. KANE:
12 Q. Dr. Sankar, I wanted to look back at your
13 declaration a bit. So if we look at the table of
14 contents at the very beginning this declaration
15 summarizes all the opinions you're offering in this
16 matter; correct?
17 A. Yes.
18 Q. And so Roman X says, "Ground 1, claims 22
19 and 25 to 31 are not anticipated by Zhang." Do you see
20 that?
21 A. Uh-huh.
22 Q. So you're offering that opinion?
23 A. Yes.
24 Q. And then Roman XI is "Ground 2, claims 22
25 and 25 to 31 are not obvious in view of Zhang." You're

1 offering that opinion?
2 A. Yes.
3 Q. Roman XII, "Ground 3, claims 22 and 25 to 31
4 are not obvious in view of Zhang, Saporito P1 and
5 Saporito P2." Do you see that?
6 A. Yes.
7 Q. And you're offering that opinion?
8 A. Yes.
9 Q. And then Roman XIII is "Ground 4, claims 22
10 and 25 to 31 are not obvious over Zhang, Marinus Orphan
11 Drug press release and Marinus phase 1 press release."
12 Do you see that?
13 A. Correct.
14 Q. You're offering that opinion?
15 A. Yes.
16 Q. And those are all the opinions you're
17 offering in this case?
18 A. Yes.
19 Q. You're not offering any opinions with
20 respect to enablement?
21 A. No.
22 Q. Are you familiar with the concept of
23 enablement in patent law?
24 A. No. Explain that to me.
25 Q. If you're not offering the opinion that's

1 all I need to know. Let's turn to page 22 of that
2 declaration. And you see there on page 22, Roman VIII
3 there's a section entitled "Claim construction"?
4 A. Uh-huh.
5 Q. And you say in paragraph 58 of a POSA,
6 P-O-S-A -- what is a POSA?
7 A. A person ordinarily skilled in the art.
8 Q. You say, "A POSA would have understood that
9 the phrase treating status epilepticus comprising
10 administering to a patient in need thereof in claims 22
11 and 25 to 31 means, quote, treating a human patient
12 suffering from SE," end quote. Do you see that?
13 A. Yes.
14 Q. So all of your opinions are based upon that
15 interpretation of the claims?
16 A. Yes.
17 Q. And that's your opinion -- well, do you
18 agree with me that there's no human data provided for
19 treatment of SE with ganaxolone in the 817 patent?
20 MS. PEHRSON: Objection. Vague.
21 THE WITNESS: Yes.
22 BY MR. KANE:
23 Q. Your understanding or interpretation of the
24 claims is that it's limited to human?
25 A. The claims made are proposing human, yeah.

1 They refer to patient.
2 Q. If we look at I think paragraph 18 of your
3 declaration you refer to -- paragraph 19, I'm sorry.
4 On page 13 of 68.
5 A. Uh-huh. Page 13.
6 Q. You refer to Exhibit 2003; correct?
7 A. Do I have the same document? This is in the
8 declaration; correct? Page 15.
9 Q. Page 13 of 68 in paragraph 19.
10 A. Oh, you know what? I'm looking at page 19.
11 There are two different paginations.
12 Q. I know. It's confusing.
13 A. Got it. Page 13 of 68, yes.
14 Q. And you see there in paragraph 19 you refer
15 to Exhibit 2003 which is a paper published in
16 Epilepsia?
17 A. Yes.
18 Q. I'm going to hand you what's been marked as
19 Exhibit 2003. So this is the paper that you are
20 discussing in your declaration?
21 (Exhibit 2003 was marked for identification
22 by the Reporter.)
23 THE WITNESS: Yes.
24 BY MR. KANE:
25 Q. And if we look at page 2 of that paper, the

1 intro, the first paragraph talks about SE. Do you see
2 that?
3 A. Yes.
4 Q. It says it's a neurological emergency;
5 correct?
6 A. Yes.
7 Q. Do you agree with that?
8 A. Yes, I do.
9 Q. And that SE is associated with substantial
10 morbidity and mortality?
11 A. Yes.
12 Q. And you see in -- actually, let's go back to
13 the patent. I'm sorry.
14 A. Okay.
15 Q. I want to look at the claims.
16 A. Page 26?
17 Q. Yeah. So the opinions you've offered are
18 with respect to claim 22 and 25 to 31 as we indicated
19 earlier?
20 A. Yes.
21 Q. It's on page 27. Column 40.
22 A. Uh-huh.
23 Q. If you look at claim 22 is there any dosing
24 regimen incorporated into claim 22?
25 MS. PEHRSON: Objection to the extent it calls

1 for a legal conclusion.
2 THE WITNESS: Claim 22 is wherein the
3 pharmaceutical composition provides improvement to the
4 patient. I think all the doses are coming down,
5 further down.
6 BY MR. KANE:
7 Q. You understand the concept of independent
8 claims and dependent claims in patents?
9 A. Not in the context of patents.
10 Q. If you look at claim 21, it's a "method of
11 treating status epilepticus, comprising administering
12 to a patient in need thereof, a pharmaceutical
13 composition comprising ganaxolone or a pharmaceutically
14 acceptable salt thereof, wherein the pharmaceutical
15 composition is administered intravenously." You see
16 that?
17 A. Yeah.
18 Q. That's what we would refer to as an
19 independent claim.
20 A. Okay.
21 Q. And then claim 22 you'll see it says, "The
22 method of claim 21," so everything that's described in
23 claim 21 --
24 A. Depending on that.
25 Q. Yeah. And where it provides the language

1 there with respect to the improvement. Do you see
2 that?
3 A. Yeah.
4 Q. Okay. But in that context then there's no
5 dosage regimen described in claim 22 or incorporated
6 into claim 22; correct?
7 MS. PEHRSON: Same objection.
8 THE WITNESS: Yeah, as stated, no.
9 BY MR. KANE:
10 Q. And then claim 25 says, "The method of claim
11 21," again, so it's a depending from claim 21, "wherein
12 the patient is administered about 500 milligrams to
13 about 1,000 milligrams per day ganaxolone." Do you see
14 that?
15 A. Yes.
16 Q. So that provides a range of daily doses;
17 correct?
18 A. Correct.
19 MS. PEHRSON: Objection. Calls for a legal
20 conclusion.
21 BY MR. KANE:
22 Q. Does it provide any more detail than that?
23 MS. PEHRSON: Same objection.
24 THE WITNESS: No. I think I would just say
25 that's what it says. What's written there.

1 BY MR. KANE:
2 Q. Could that be a single dose of 500 to --
3 500 milligrams to 1,000 milligrams in a 24-hour period?
4 MS. PEHRSON: Objection. Vague.
5 THE WITNESS: It doesn't say that here. It says
6 elsewhere that it could be twice a day, three times a
7 day. That's a number of options that's been covered
8 but not in this particular statement. It just refers
9 to the daily dose.
10 BY MR. KANE:
11 Q. So it would cover all the options as long as
12 they fell within that range?
13 MS. PEHRSON: Objection. Calls for a legal
14 conclusion.
15 MR. KANE: Why don't you read back the question.
16 (Record read.)
17 THE WITNESS: Yes.
18 BY MR. KANE:
19 Q. And then claim 26 says, "The method of claim
20 21 wherein the patient is administered about
21 625 milligrams to about 650 milligrams per day
22 ganaxolone." Do you see that?
23 A. Yes, I do.
24 Q. So again other than the range does it
25 provide any detail with respect to the dosing regimen?

1 MS. PEHRSON: Same objections.
2 THE WITNESS: It just has a number of separate
3 claims bracketing a range of doses.
4 BY MR. KANE:
5 Q. So just for instance in claim 26 it could be
6 one dose of between 625 milligrams per day and
7 650 milligrams per day?
8 A. It could be one dose or it could be multiple
9 doses. It's not specified here.
10 Q. Could it be a continuous IV drip?
11 MS. PEHRSON: Objection. Calls for a legal
12 conclusion.
13 THE WITNESS: It could be.
14 BY MR. KANE:
15 Q. And is the same true for all the claims 27
16 to 31 that they provide ranges but not any more detail?
17 MS. PEHRSON: Same objection.
18 THE WITNESS: Yes.
19 BY MR. KANE:
20 Q. So claim 30 says, "The method of claim 21
21 wherein the patient is administered about 700 to
22 725 milligrams per day." Do you see that?
23 A. Uh-huh.
24 Q. So again, there's no more specificity other
25 than the daily range?

1 MS. PEHRSON: Same objection.
2 THE WITNESS: Yes.
3 BY MR. KANE:
4 Q. So now let's look at Exhibit 2003, the
5 Marinus publication. If we look at paragraph 2.2 on
6 page 3 of 11.
7 A. Which page again?
8 Q. Page 3 of 11. Paragraph 2.2. You see
9 there's a section entitled "Treatment"?
10 A. Yes.
11 Q. And it says here, "The patients received IV
12 ganaxolone in addition to ongoing treatment with second
13 line IV ASMs." Do you see that?
14 A. Yes.
15 Q. What are ASMs?
16 A. Antiseizure medications.
17 Q. What does it mean to be a second line?
18 A. As I mentioned earlier the first line is
19 usually benzodiazepine. The second line typically is
20 either levetiracetam, fosphenytoin, or valproate acid
21 one of the three commonly used second line medications.
22 Q. Once the patient has progressed to a second
23 line medication is the first line medication stopped?
24 MS. PEHRSON: Objection.
25 THE WITNESS: Mostly it's a one shot deal but

1 occasionally people may go back to more of it.
2 BY MR. KANE:
3 Q. When you say one shot deal what do you mean?
4 A. Usually, yeah, it progresses, the Ativan is
5 given once but it may be repeated. Sometimes because
6 they conservatively dosed it but they're not sure how
7 the patient is going to respond, but once they conclude
8 it's not producing the result they go to second line.
9 Q. And they stop the Ativan for instance?
10 A. At that point, yeah.
11 Q. So these patients you understand in this
12 study were receiving the second line IV ASM?
13 A. Correct.
14 Q. And then ganaxolone was added to that
15 therapy?
16 A. Yeah.
17 Q. It states there that the formulation of
18 ganaxolone used in this trial was solubilized using
19 Captisol. Do you know have any familiarity with what
20 Captisol is?
21 A. Yes.
22 Q. What is that?
23 A. It's a commonly available solubilizing
24 agent. It makes a somewhat fatty compound go into a
25 watery thing.

1 Q. Have you had experience with Captisol in
2 your practice?
3 A. I don't use Captisol. It's more of a
4 pharmaceutical preparation. It's not something we
5 clinically resort to. But we play get a product that's
6 in Captisol.
7 Q. So you understand that this formulation of
8 ganaxolone was in Captisol?
9 A. Yes.
10 Q. And you see there it says that there's a
11 daily exposure limit of up to 50 grams per day?
12 A. Yes.
13 Q. Do you understand why there's a limit on
14 Captisol?
15 MS. PEHRSON: Objection. Foundation.
16 THE WITNESS: I couldn't tell you offhand how
17 they came up with that dose. That would be
18 recommendations from the FDA based on safety studies.
19 BY MR. KANE:
20 Q. And you see about a sentence down there that
21 begins, "Because no patients weighed less than
22 40 kilograms, ganaxolone was studied in the following
23 three dose cohorts: 500 milligrams per day, low,
24 650 milligrams per day, medium, and 713 milligrams per
25 day, high, the most ganaxolone that can be administered

1 while staying within the Captisol time limit shown in
2 Figure 1." Do you see that?
3 A. Right.
4 Q. So all the patients in the study were
5 greater than 40 kilograms?
6 A. Yes.
7 Q. And they were divided into these three dose
8 cohorts?
9 A. Yeah.
10 Q. And Figure 1 on the next page, page 4, is
11 the dosing or trial flow diagram I guess it's referred
12 to?
13 A. Yeah.
14 Q. And then you see continuing back on page 3
15 in the treatment section it says, "In all dose cohorts
16 ganaxolone infusion was initiated as an IV bolus over
17 three minutes."
18 A. Yeah, I see that.
19 Q. And then it continues on "with continuous
20 infusion of decreasing infusion rates for 48 to 96
21 hours followed by an 18-hour taper," and then it says,
22 "See Table 1 for details"; correct?
23 A. Yes.
24 Q. So when it says "an IV bolus over three
25 minutes," what do you understand that to mean?

1 A. It means that dose is given over three
2 minutes as an infusion.
3 Q. Do you know what the size of the bolus was?
4 A. I don't know the volume. It's not specified
5 here. But we could probably compute it based on the
6 concentration if they have it.
7 Q. And what do you understand when it says
8 "continuous infusion of decreasing infusion rates for
9 48 to 96 hours" to mean?
10 A. It's basically an hourly rate that is
11 gradually being turned down.
12 Q. And then it says "an 18-hour taper." What
13 do you understand that to be?
14 A. Meaning during that time you're gradually
15 reducing it, not abruptly stopping but gradually
16 reducing the drip rate.
17 Q. It continues. Then it says, "These infusion
18 parameters allow for rapid loading of ganaxolone
19 (plasma concentration) of approximately 900 nanograms
20 per ml designed to abort SE followed by maintenance
21 doses aimed at sustaining seizure control." Do you see
22 that?
23 A. Yes.
24 Q. What do you understand when it talks about
25 the "rapid loading of ganaxolone"?

1 A. It's to achieving a therapeutic level
2 promptly.
3 Q. And why is that important?
4 A. Because status is an emergency. You want to
5 gain control of it.
6 Q. And is that why it's important to use the
7 three-minute bolus?
8 A. Yes. You want to achieve the blood level
9 quickly and then you try to maintain the drip rate.
10 Q. And you see it says, "If in the opinion of
11 the investigator the patient was deriving continuing
12 benefit, ganaxolone infusion could be extended for an
13 additional 48 hours to a total of 96 hours."
14 A. Correct.
15 Q. So the -- up above it says, "The decreasing
16 infusions are 46 to 98 hours." You see that?
17 A. Yes.
18 Q. Do you understand that to be the study was
19 set up for an initial 48-hour period which could be
20 extended by the physician?
21 A. Correct.
22 Q. And if we look at Figure 2 on the next page,
23 page 4 of 11, you see that's described as "modeled
24 pharmacokinetic curve for all groups." You see that?
25 A. Yeah.

1 Q. And do you see that there appears to be a
2 spike up to approximately 900 nanograms per ml?
3 A. Yes.
4 Q. And do you understand that to result from
5 the bolus that's provided?
6 A. Correct.
7 Q. If you didn't provide the bolus would you
8 get that type of spike?
9 MS. PEHRSON: Objection. Foundation.
10 THE WITNESS: You won't without a bolus.
11 BY MR. KANE:
12 Q. If you look at Figure 3 it's described as
13 "Effects of ganaxolone infusion on seizure in patients
14 with RSE." Do you see that?
15 A. I see.
16 Q. And just so it's clear, what do you
17 understand RSE to be there?
18 A. Refractory status epilepticus.
19 Q. And what does that refer to?
20 A. It refers to the fact that the status did
21 not respond to second line therapy and they went to
22 ganaxolone.
23 Q. And if we look at the Figure B of -- well,
24 3 --
25 A. 3B.

1 Q. Yes, 3B. It describes the low, medium and
2 high dose cohorts; correct?
3 A. Yes.
4 Q. And at times zero, there's what's referred
5 to as GNX initiation?
6 A. Correct.
7 Q. And GNX refers to ganaxolone?
8 A. Yes.
9 Q. And what do you understand is occurring then
10 at times zero or shortly thereafter?
11 A. Shortly thereafter the seizure burden comes
12 down dramatically as quantified by EEG.
13 Q. And is that because the bolus had been
14 delivered?
15 A. Correct.
16 Q. And then what do you glean as the time
17 progresses?
18 MS. PEHRSON: Objection. Vague. Foundation.
19 THE WITNESS: As time -- again, these are small
20 numbers so I wouldn't quantitatively interpret it, but
21 you can see during the first four hours even the group
22 that got medium tends to have more seizure activity
23 than the ones on either the low or high. But if you
24 look at about eight hours the low also develops a great
25 deal of EEG activity again and the high dose remains

1 quite controlled with very low EEG activity up to
2 14 hours.
3 BY MR. KANE:
4 Q. Do you understand why the medium dose seems
5 to have increased seizure activity relatively early on?
6 MS. PEHRSON: Objection. Foundation.
7 THE WITNESS: Yeah, one could only speculate,
8 you know. These are studies with a very small number
9 of patients and they all may not have had the same
10 course. We just may have segregated into the medium
11 dose, a set that behaved in a particular way.
12 BY MR. KANE:
13 Q. And in forming your opinions did you attempt
14 to understand the exact amounts in the bolus and the
15 tapering of the infusion after the bolus was delivered?
16 A. Only to the extent they describe it.
17 Q. When you say the extent they describe it you
18 just mean the three dose cohorts, the 713, the 650 and
19 the 500?
20 A. Correct.
21 Q. Coupled with the description of the bolus
22 for three minutes?
23 A. Yes.
24 Q. But no more than that?
25 A. Yeah.

1 Q. No more than that?
2 A. And then the infusion, that was also --
3 because it continues infusion followed by that.
4 Q. Right. But do you have any details of the
5 continuous infusion?
6 A. They give a range.
7 Q. Where do you see the range?
8 A. In the treatment side. They don't quite
9 give you a specific details here. It says go to table
10 for details. The reason we don't see it because it
11 says look at Table S1. You'll have to go to the
12 website. It's a supplemental. People don't always
13 publish everything. Some things are available for
14 inspection as supplemental data that's not in the
15 print.
16 Q. Did you review Table S1 in forming your
17 opinions?
18 A. No, I didn't.
19 Q. If we look back at Figure 2 on page 4 of 11
20 you see the predicted GNX plasma concentration level?
21 A. Yes.
22 Q. And you see that the three dose cohorts have
23 different plasma concentrations?
24 A. Correct.
25 Q. And do the different plasma concentrations

1 explain the different seizure activity in the
2 patient -- or in the animals?
3 MS. PEHRSON: Objection. Vague. Foundation.
4 THE WITNESS: Not entirely because as you can
5 see between 12 and 24 hours they're fairly stable. But
6 these are just computer simulations.
7 BY MR. KANE:
8 Q. Right.
9 A. They do not measure concentrations.
10 Q. Understand but if we look at Figure 3 and we
11 see the 3B we talked about earlier, you see different
12 seizure burden on the animals; correct?
13 A. Yes.
14 Q. Is that related to the plasma
15 concentrations?
16 MS. PEHRSON: Objection. Foundation.
17 THE WITNESS: It's not a linear correlation
18 here. It's not a linear correlation between these
19 blood levels and that.
20 BY MR. KANE:
21 Q. But how do the plasma levels impact the
22 seizure burden?
23 MS. PEHRSON: Objection. Foundation.
24 THE WITNESS: Plasma levels would have benefit
25 depending on the level but it's not the only variable.

1 The patient may be demonstrating an EEG activity
2 depending also on the cause of any other medications,
3 seizures, regular seizure medications they're on. It
4 may indicate to some agree what caused the SE in the
5 first place. We generally expect that these groups
6 would have a lot of variability.
7 BY MR. KANE:
8 Q. Well, in this study, this is a rat
9 pilocarpine model.
10 A. This is patients.
11 Q. You're right. I'm sorry.
12 A. It's not rat pilocarpine.
13 Q. I'm sorry. You are correct.
14 A. You couldn't give that dose to a rat.
15 Q. Fair enough. Fair enough. If we look at
16 page 8 of 11 -- well, before we get there, if you
17 change the dosing regimen so you had different plasma
18 levels would you expect the patients to respond
19 differently?
20 MS. PEHRSON: Objection. Foundation. Vague.
21 THE WITNESS: You might hope but there's too
22 much variability in patients.
23 BY MR. KANE:
24 Q. Would you expect patients to respond the
25 same to different dosing regimens?

1 MS. PEHRSON: Objection. Foundation. Vague.
2 THE WITNESS: It's a very difficult thing to say
3 because let's say hypothetically a patient responds to
4 10 milligrams of something. Would they respond to two
5 different doses while they're on 12 or 14? They may
6 respond similarly because they have surpassed the
7 expected dose but if they're on 8 or 6 they may not.
8 BY MR. KANE:
9 Q. And to some extent Figure 3 illustrates that
10 point and as you pointed out earlier the high dose
11 cohort had seizure control, significant seizure control
12 past the 8-hour mark?
13 A. Right.
14 Q. Whereas the low and medium --
15 A. Did not.
16 Q. And likewise you indicated that the very
17 rapid decrease in seizure activity shown there near
18 times zero is as a result of the bolus dose?
19 MS. PEHRSON: Objection to the extent it
20 mischaracterizes his prior testimony.
21 THE WITNESS: Presumably.
22 BY MR. KANE:
23 Q. Well, what else would explain it?
24 MS. PEHRSON: Objection. Foundation.
25 THE WITNESS: Sometimes you don't know if the

1 innate status is winding down on its own for other
2 reasons.
3 BY MR. KANE:
4 Q. If we look at page 8 of 11 at the second
5 paragraph they concluded, "These data support that the
6 ganaxolone regimen administered in the high dose cohort
7 (713 milligrams per day) may reduce or prevent
8 escalation of care to third line IV anesthetics." Do
9 you see that?
10 A. Yes, I do.
11 Q. And it says -- it continues on beginning of
12 the next sentence it says, "This is clinically
13 significant." Do you see that?
14 A. Yes.
15 Q. Do you agree with that?
16 A. I agree totally.
17 Q. If you go to the next paragraph --
18 A. The one that begins, "It is notable that
19 ganaxolone" --
20 Q. Yes. It describes there that "It's notable
21 that ganaxolone was shown to control seizure activity
22 whether the patients presented with or without
23 convulsions." Do you see that?
24 A. Yes.
25 Q. And then it describes some of the animal

1 studies and continues on to say, "It's important to
2 note that the SE did not reoccur in the majority of
3 patients even after discontinuation of ganaxolone
4 infusions." Do you see that?
5 A. Yes.
6 Q. And why is that important?
7 MS. PEHRSON: Objection. Foundation.
8 THE WITNESS: It suggests that the effect was
9 lasting.
10 BY MR. KANE:
11 Q. And --
12 A. Durable.
13 Q. And then it continues, the next sentence
14 says, "Only 3 patients (18 percent) required an
15 additional second line IV ASM for SE treatment in the
16 24 hours following tapering and discontinuation of
17 ganaxolone." Do you see that?
18 A. Yes.
19 Q. And you understand that means that even
20 patients in the low and medium dose cohort did not
21 require or the vast majority did not require the second
22 line ASM?
23 A. Correct. In this statement they don't
24 specify what dose these patients required, the ones
25 that went on to receive further treatment.

1 Q. And so the patients that were in the low and
2 medium dose cohort as we see here in Figure 3B
3 benefited even though their seizure activity was not as
4 controlled as the high dose cohort?
5 MS. PEHRSON: Objection. Vague. Foundation.
6 THE WITNESS: Presumably. It's hard to know
7 that when they got the second line IV again that they
8 may have responded better because they had received
9 ganaxolone previously, but it was hard to speculate on
10 that.
11 BY MR. KANE:
12 Q. Well, I guess I'm looking at the sentence,
13 I'm not sure what you mean by that because it says, "In
14 the 24 hours following the discontinuation only three
15 (18 percent) required that second line therapy";
16 correct?
17 A. Correct.
18 Q. So that means patients in the low and medium
19 dose cohort, at least in that first 24-hour period
20 after ganaxolone, the majority of them did not require
21 a second line?
22 A. Correct.
23 Q. So they benefited from ganaxolone?
24 A. Yes.
25 MS. PEHRSON: Objection. Vague. Foundation.

1 BY MR. KANE:
2 Q. And then it continues on to say, "Reductions
3 in seizure burden occurred rapidly in all three
4 ganaxolone dose cohorts." Do you see that?
5 A. Yes.
6 Q. And we talked about that a couple of times,
7 that's the function of the bolus?
8 A. Yes.
9 Q. And then it says, "Patients in the high dose
10 cohort maintain ganaxolone plasma concentrations
11 greater than 500 nanograms per ml for eight hours
12 following treatment initiation and demonstrated the
13 most durable reductions in seizure burden"; correct?
14 A. Yes.
15 Q. So only the high dose cohort maintained the
16 500 nanograms per ml for eight hours?
17 A. Yes.
18 Q. And that was the most durable treatment?
19 MS. PEHRSON: Objection. Foundation.
20 THE WITNESS: Yes, that's what they specify
21 here.
22 BY MR. KANE:
23 Q. And that 500 -- the 500 nanogram per ml
24 plasma concentrations is a function of the dosing
25 regimen?

1 A. It's the result of the bolus but not
2 everybody will get the same blood level. It depends
3 also on the patient's factors pertaining to an
4 individual patient.
5 Q. Well, it's a function of the bolus and then
6 the continuous infusion afterwards?
7 A. Yes.
8 Q. Because only the high dose patients maintain
9 that level; correct?
10 A. Correct.
11 Q. And of course the high dose patients we saw
12 had the greatest control of seizure activity?
13 A. Yes.
14 Q. And then they continue on to say, "Although
15 not studied in the present trial maintaining ganaxolone
16 levels greater than 500 nanograms per ml for durations
17 longer than eight hours may offer additional benefit
18 that will be evaluated in future clinical studies";
19 right?
20 A. Yes.
21 Q. So what do you understand the importance of
22 the 500 nanogram per ml level to be?
23 MS. PEHRSON: Objection. Vague.
24 THE WITNESS: It's a suggestion that one should
25 maintain patients in that level and possibly for a

1 longer duration as they speculate.
2 BY MR. KANE:
3 Q. If you turn to your declaration, Dr. Sankar,
4 page 47 of 68 -- actually page 48 of 68. I'm sorry.
5 The next page. So in paragraph 109 you're referring to
6 the article that we were just looking at describing the
7 phase 2 which is Exhibit 2003; correct?
8 A. Yes.
9 Q. And then in paragraph 110 you say, "All
10 three dose cohorts met the primary end point. No
11 patient who received ganaxolone added to the standard
12 of care ASMs required treatment with IV anesthetics
13 within 24 hours of ganaxolone initiation." Do you see
14 that?
15 A. Yes.
16 Q. If you change the dosing regimen would you
17 necessarily expect that all patients would achieve that
18 end point?
19 MS. PEHRSON: Objection. Foundation.
20 THE WITNESS: That's speculative.
21 BY MR. KANE:
22 Q. So for instance if you limited the bolus
23 would you think that the patients would achieve that
24 end point?
25 MS. PEHRSON: Objection. Foundation.

1 THE WITNESS: My suspicion is they would not
2 have been controlled as rapidly.
3 BY MR. KANE:
4 Q. Would they have been controlled at all?
5 MS. PEHRSON: Objection. Calls for speculation.
6 THE WITNESS: Potentially.
7 BY MR. KANE:
8 Q. You don't know?
9 A. You don't know until you actually do that.
10 Q. So changing the dosing regimen could change
11 the results?
12 A. Yes.
13 Q. If you look at paragraph 114 of your
14 declaration on page 50 of 68?
15 A. The phase 2 clinical study?
16 Q. Yes. You say, "Was particularly unexpected
17 for the dose range recited in claim 30 (i.e.,
18 700 milligrams to 725 milligram per day ganaxolone";
19 correct?
20 A. Yes.
21 Q. And then you see at the end of that you're
22 referring to Exhibit 2007 and 2008?
23 A. Yes.
24 Q. I'll hand you what's been marked as Exhibit
25 2008.

1 (Exhibit 2008 was marked for identification
2 by the Reporter.)
3 BY MR. KANE:
4 Q. If you look at page 27 of this document is
5 what you're referring to? 27 of 60.
6 A. Yes.
7 Q. And actually if we go back to page 25 of 60
8 just to orient ourselves.
9 A. Yes.
10 Q. You see there this is a declaration under
11 37CFR, Section 1.132; correct?
12 A. Yeah.
13 Q. And the declaration is made by Joseph
14 Hulihan, M.D. Do you see that?
15 A. Yes.
16 Q. Do you know Dr. Hulihan?
17 A. I do.
18 Q. And how do you know Dr. Hulihan?
19 A. I've known him for probably three decades.
20 He used to be in charge of the development of a
21 medication called topiramate or Topamax for J&J many,
22 many years ago. So we worked together on a number of
23 things for probably at least a decade on that product.
24 Q. And I guess what's your opinion of
25 Dr. Hulihan?

1 A. What's the question?
2 Q. What's your professional opinion of
3 Dr. Hulihan?
4 A. Dr. Hulihan is a very competent person with
5 substantial experience in drug development.
6 Q. If we look at the next page, page 26 out of
7 60, paragraph 5, again, sort of repeating some of the
8 things we've heard early but "SE is a medical emergency
9 requiring urgent care to avoid permanent brain damage,
10 medical compilations or death." Do you see that?
11 A. Yes.
12 Q. Do you agree with that?
13 A. I do.
14 Q. He continues, "SE is a rare condition for
15 which there are a paucity of evidence-based
16 treatments." Do you agree with that?
17 A. Yes.
18 Q. He then continues at the next sentence, "The
19 clinical objective in treating SE is to administer
20 therapy to stop the seizures as quickly and as safely
21 as possible."
22 A. Correct.
23 Q. And then, "A key objective is that the
24 medication be administered for a limited duration to
25 stop the seizures and if the effect lasts beyond

1 discontinuation of the medication." Do you see that?
2 A. Yes.
3 Q. Do you agree with that?
4 A. Yes.
5 Q. And finally he continues and says, "That is
6 a treatment that can break the status and restore the
7 brain to normal state of activity without recurrence of
8 seizures when the medication is discontinued."
9 A. Agreed.
10 Q. And that terminology of "break" is commonly
11 used?
12 A. Yes, it is.
13 Q. In paragraph 6 he talks about the use of
14 intervenous anesthetic drugs to stop seizures. Do you
15 see that?
16 A. Yes.
17 Q. And he says, "The comatose state is
18 typically maintained for 24 to 48 hours after which the
19 anesthetic drug is tapered to determine if SE has been
20 terminated." Do you see that?
21 A. Yes. This is quite consistent with what I
22 told you earlier.
23 Q. Right?
24 A. You check overnight.
25 Q. And as you said earlier, he says, "However,

1 seizures frequently return when the drugs are
2 withdrawn"?
3 A. Yes.
4 Q. So this is all consistent with your
5 understanding and experience?
6 A. Yes.
7 Q. Then if we look at paragraph 8 on page 27 of
8 60. So Dr. Hulihan states there, "In our clinical
9 investigations we unexpectedly discovered that SE could
10 be rapidly and persistently suppressed using less
11 ganaxolone and for a much shorter period of time that
12 was anticipated." Do you see that?
13 A. Yes.
14 Q. And then he says, "We determined that
15 administering ganaxolone as an intravenous bolus and
16 continuous intravenous infusion to achieve and maintain
17 a ganaxolone plasma concentration of about 500
18 nanograms per ml to about 1,000 nanograms per ml for
19 about eight to 12 hours resulted in rapid and
20 persistent suppression of SE without recurrence of SE
21 when the rate of ganaxolone infusion was reduced and
22 the treatment was terminated"; right?
23 A. Yes.
24 Q. So the unexpected result here is tied to the
25 plasma concentrations?

1 MS. PEHRSON: Objection. Foundation. Vague.
2 THE WITNESS: I think the unexpected aspect of
3 this was partly that even a short duration of the
4 infusion was so effective.
5 BY MR. KANE:
6 Q. The eight to 12 hours?
7 A. Yeah.
8 Q. But the eight to 12 hours is tied to a
9 concentration of between 500 nanograms to about 1,000
10 nanograms per ml; correct?
11 A. Correct.
12 Q. And in fact in paragraph 9 he continues to
13 say, "Our investigations also surprisingly revealed
14 that targeting a transient ganaxolone plasma
15 concentration of about 500 to about a thousand
16 nanograms per ml was not enough to result in persistent
17 suppression of SE"; correct?
18 A. Yes, correct.
19 Q. And then he continues in 9, "We found it was
20 important to maintain that ganaxolone plasma
21 concentration for about eight to 12 hours to achieve
22 persistent suppression"; right?
23 A. Correct.
24 Q. So that means that if you don't maintain
25 that plasma concentration for eight to 12 hours you do

1 not get the persistent suppression?
2 MS. PEHRSON: Objection. Foundation. Vague.
3 THE WITNESS: Seizures occur.
4 BY MR. KANE:
5 Q. Right. In fact, he says, "In fact, when the
6 plasma concentration dropped below 500 nanograms per ml
7 prior to completing eight to 12 hours of treatment
8 seizures rapidly recurred"; right?
9 A. Correct.
10 Q. And then, "It was completely unexpected that
11 providing ganaxolone at a serum concentration of about
12 500 nanograms per ml to about a thousand nanograms per
13 ml for a short duration of only about eight to 12 hours
14 result in a persistent SE suppression"; right?
15 A. Yes.
16 Q. So if you don't maintain that plasma
17 concentration of 500 nanograms per ml to about a
18 thousand nanograms per ml for eight to 12 hours you
19 don't get suppression; right?
20 MS. PEHRSON: Objection. Foundation.
21 BY MR. KANE:
22 Q. So if I did a dosing regimen of ganaxolone
23 that did not achieve those plasma concentrations, you
24 would not expect SE suppression, correct?
25 MS. PEHRSON: Objection. Foundation. Form.

1 THE WITNESS: Based on this limited trial. It's
2 a very short, small population non-randomized trial.
3 BY MR. KANE:
4 Q. But that's what his declaration says?
5 A. Right.
6 Q. And if you look at the footnote on 1 it
7 says, "The high dose produced a ganaxolone plasma
8 concentration of about 500 nanograms to about 1,000
9 nanograms for about eight hours while the low dose and
10 medium dose did not achieve this plasma concentration
11 for the eight-hour period"; right?
12 A. Correct.
13 Q. And Dr. Hulihan states up in paragraph 9
14 that if you don't maintain that concentration for that
15 period of time seizures rapidly recur; right?
16 A. Correct.
17 Q. Let's look back at your declaration. I'm
18 sorry I keep going back and forth.
19 A. That's okay.
20 Q. If you look at paragraph 105 -- actually
21 let's look at paragraph 98 first. It's on page 44 of
22 68.
23 A. Yes.
24 Q. And again, and just to orient what we're
25 talking about here, if you look at page 41 of 68 we

1 have Roman XI.
2 A. Yes.
3 Q. And this is where you're offering the
4 opinion that claims 22 and 25 are not obvious in view
5 of Zhang; correct?
6 A. Yes.
7 Q. And then in paragraph 98 you have a
8 conclusion in this section where you state, "As
9 described above, there's no reason that a POSA would
10 have a reasonable expectation of success that the
11 administration of the full dose of ganaxolone broken
12 into multiple repeated administrations would result in
13 an improvement to the patient after administration for
14 more than eight hours if a single administration of the
15 full dose for SE suppresses seizures for up to two
16 hours"; correct?
17 A. Correct.
18 Q. And when we talk about the patient there
19 that's a human patient?
20 A. For a POSA it always means a human patient,
21 yes.
22 Q. And the next section is claims 25 to 31
23 would not have been obvious in view of Zhang. Do you
24 see that?
25 A. Yes.

1 Q. And at the end of that if you look at the
2 section, I believe in paragraph 106 is your conclusion.
3 You state, "Therefore based on Zhang's disclosure of
4 POSA would not have had a reasonable expectation of
5 success in treating a human patient suffering from SE
6 with the doses recited in claims 25 to 31"; correct?
7 A. Yes.
8 Q. And it's explicitly saying a human patient?
9 A. The Zhang paper doesn't refer to human
10 patient.
11 Q. Right. But your opinion is based on the
12 understanding of --
13 A. Expectation of a human patient; yes.
14 Q. If you turn to paragraph 123 which is on
15 page 54 of 68 and there's a section Roman XII, "Ground
16 3, claims 22 and 25 to 31 are not obvious in view of
17 Zhang Saporito P1 and Saporito P2." Do you see that?
18 A. Yes.
19 Q. And paragraph 125 the next page you state as
20 you just said, "Zhang does not describe intravenously
21 administering to a human patient"; correct?
22 A. Correct.
23 Q. And then you say in paragraph 126, "Saporito
24 P1 and P2 do not describe intravenously administering
25 to a human patient"; correct?

A. Correct.
Q. So then in paragraph 128 you again reach your conclusion, "That neither Saporito P1 nor Saporito P2 discloses intravenously administering ganaxolone to a human patient suffering from SE"; correct?
A. Correct.
Q. And based on that understanding you say, "A POSA would have understood that no combination of Zhang, Saporito P1 and Saporito P2 discloses, quote, treating status epilepticus comprising administering to a patient in need thereof under the correct construction"; right?
A. Correct.
Q. So it's your view that absent human data the patent cannot claim treating a human patient?
MS. PEHRSON: Objection. Foundation. That mischaracterizes his opinion.
THE WITNESS: It would seem that way to me. I'm not a patent specialist.
BY MR. KANE:
Q. That's your understanding?
A. That's my understanding.
Q. And if we look at paragraph 136 which is on page 59 of 68 there is description there of the Saporito P1 poster that discloses a survival rate at 24

1 hours plus; correct?
2 A. Correct.
3 Q. And that's similar to what we saw in the 817
4 patent?
5 A. Yes.
6 Q. And you say there that, at the end, "A POSA
7 would not -- would have understood that the 24-hour
8 survival rate of rats as reported in Saporito P1 does
9 not necessarily suggest improvement in treating SE in
10 humans after eight hours"; correct?
11 A. Correct.
12 Q. And so again, you're drawing the distinction
13 between the data in rats versus humans?
14 A. Absolutely. You have probably heard that
15 many disorders have been treated many, many times in
16 mice and they're far from that in humans.
17 Q. Unfortunately sometimes; right?
18 A. Yeah.
19 MR. KANE: We're a little past an hour again.
20 Do you want to take lunch now?
21 THE WITNESS: It's up to you.
22 MR. KANE: Let's take a lunch break now.
23 (At the hour of 11:53 A.M., there was a
24 luncheon recess taken.)
25

1 (At the hour of 1:03 P.M., the
2 deposition was resumed.)
3
4 EXAMINATION (RESUMED)
5 BY MR. KANE:
6 Q. Good afternoon. I wanted to touch base -- a
7 couple of things we talked about earlier this morning.
8 You mentioned you have experience with the rat
9 pilocarpine model.
10 A. Yes.
11 Q. You're familiar with drug testing where it
12 starts in animals and then proceeds to humans?
13 A. Yes.
14 Q. Have you ever been involved in dose ranging
15 studies?
16 A. In animals, yes.
17 Q. And what is a dose ranging study?
18 A. Just to test a compound to see what range it
19 begins to show the pharmacologic effect you want.
20 Q. How about in humans?
21 A. In the humans usually pharmaceutical
22 companies do that very early. Often it is done as a
23 phase 1 study when they do the dose ranging. By the
24 time I see clinical trials in a setting like UCLA
25 they're usually phase 3 studies. So the dose range has

1 already been established and they have decided on a
2 dose.
3 Q. Do you understand how the pharmaceutical
4 companies move from the animal doses to the human
5 doses?
6 MS. PEHRSON: Objection. Foundation.
7 THE WITNESS: They don't necessarily move --
8 there's no formula to go from animals to humans. They
9 pretty much have to do the phase 1 starting with a very
10 low range and see, establish tolerability and then
11 determine the pharmacokinetics.
12 BY MR. KANE:
13 Q. But is your understanding that that's a
14 standard process in drug development?
15 A. Yes.
16 Q. But you've never personally been involved in
17 a phase 1 dose ranging study?
18 A. No.
19 Q. In the work you've done say on advisory
20 boards you have seen animal study results?
21 A. They very seldom in the advisory boards come
22 up with us. The clinical advisory boards I have served
23 in, my hat is much more like a clinician. I bring
24 basic science insights. That's really quirky. I'm
25 probably the only person in the country who has a Ph.D.

1 in medicine and chemistry. The drug companies like it
2 but that's really not a typical thing. Most people are
3 not that familiar with the process. They mostly bring
4 their clinical expertise to the table in an advisory
5 board.
6 Q. In your experience would drug companies move
7 into human clinical trials if the animal models had
8 failed?
9 MS. PEHRSON: Objection. Foundation. Vague.
10 THE WITNESS: Typically for a long time they
11 didn't, however, everybody talks about it as kind of a
12 landmark. It's a limitation that our human -- that our
13 animal screening models are imperfect. They give a lot
14 of bonus points to the creativity of the company called
15 UCB with a drug you're familiar with called Keppra.
16 They actually went against what they learned from
17 animal models and used more traditional models and they
18 came up with a very successful compound.
19 So now there's been a move -- and I say now for
20 more than a decade that we need to be expanding the
21 models used. The other concern is that because we use
22 these models that are really not like human epilepsy
23 that we max out. We bring new drugs but they were
24 developed using the same screens so they turn out to be
25 not all that novel in clinical use.

1 BY MR. KANE:
2 Q. Other than that one example with UCB are you
3 familiar with any drugs that were developed when the
4 animal models did not work?
5 A. My experience is mainly in the world of
6 epilepsy. There, no. They're the only company that
7 kind of went about it differently.
8 Q. And they developed some other model?
9 A. Yeah. In the meantime new models have
10 evolved.
11 Q. In that example, the UCB example how did
12 they --
13 A. UCB used a kindling model in which -- where
14 classic models were broadly two types. One where rats
15 or mice get electric shock that puts them into a
16 convulsion and use compounds to see if they can protect
17 them from it. The other type was a chemo convulsant
18 where they're injected with a convulsive compound and
19 whether your test compound can protect. Those are the
20 two serious models that are used for a long time. They
21 go back to the early 1930s.
22 Q. And what did UCB do that was different?
23 A. UCB moved a compound along even though it
24 failed in both those models. They didn't discard them.
25 They said we're going to try yet another model called a

1 kindling model.
2 Q. What is a kindling model?
3 A. The kindling model is a very important model
4 that initially came about to understand human learning
5 and memory and that is that in certain circuits such as
6 the hippocampus if you provide a very small stimulus
7 that is not enough to produce a response, but if you
8 keep doing that at periodic intervals, over time you
9 will start getting a response and eventually a full
10 convulsive response.
11 This is because we say, we use the term the
12 synaptic efficacy is gradually increasing. It's a
13 model for learning because that's kind of how, you
14 know, you read things four times before your law school
15 boards to try to remember things; right? That each
16 reading enhances your learning. So that became an
17 important model and UCB used a model of that to how the
18 brain learns to seize.
19 Q. Would the fact that a compound had shown
20 efficacy in an animal model impact the researcher's
21 view as to whether it would work in human?
22 MS. PEHRSON: Objection. Form. Foundation.
23 Vague.
24 THE WITNESS: Historically there's no guarantee.
25 ///

1 BY MR. KANE:
2 Q. Well, there's no guarantee but does it make
3 it more likely or less likely if it works in the animal
4 model?
5 A. Well, it's a screen so it's considered more
6 likely.
7 Q. I think you mentioned earlier this morning
8 that going into the humans is expensive?
9 A. Very.
10 Q. And time consuming?
11 A. Yes.
12 Q. In your experience have you -- do most
13 pharmaceutical companies need to have some belief that
14 the compound has promise before they would expend those
15 kind of resources?
16 A. Yes.
17 MS. PEHRSON: Objection. Foundation. Vague.
18 BY MR. KANE:
19 Q. I'll hand you what's been marked as Exhibit
20 1011, Dr. Sankar.
21 (Exhibit 1011 was marked for identification
22 by the Reporter.)
23 BY MR. KANE:
24 Q. I believe this is the document that you
25 reviewed in preparing your declaration; right?

1 A. Uh-huh.
2 Q. Is that yes?
3 A. Yes.
4 Q. And you see this is dated April 15 of 2016?
5 A. Yes.
6 Q. And this is a Marinus press release?
7 A. Uh-huh.
8 Q. And you see at the end that this is
9 announcing that Marinus had received FDA Orphan Drug
10 designation for ganaxolone IV to treat status
11 epilepticus?
12 A. Yes.
13 Q. And at the last sentence of the first
14 paragraph says, "A phase 1 clinical trial evaluating
15 the safety, tolerability and pharmacokinetics of
16 ganaxolone IV is expected to initiate in the first half
17 of 2016"?
18 A. Yes.
19 Q. Do you understand from that, that by early
20 2016 Marinus was pursuing ganaxolone treatment for SE?
21 A. Yes.
22 Q. And since they were going into the phase 1
23 clinical trial they had some expectation that it was
24 going to be effective in treating humans?
25 MS. PEHRSON: Objection. Foundation. Vague.

1 THE WITNESS: I can't comment on what their
2 thoughts were, but it seems logical that it was a
3 promising approach to that, otherwise they wouldn't
4 have gone into phase 1.
5 BY MR. KANE:
6 Q. Earlier this morning we talked about some of
7 the patients you've seen where they sort of go in and
8 out of status; correct?
9 A. Correct.
10 Q. Do the patients benefit despite having the
11 status or the seizure activity reduced for a period of
12 time even if it may ultimately come back?
13 MS. PEHRSON: Objection. Vague. Foundation.
14 THE WITNESS: That's generally not our goal of
15 treatment.
16 BY MR. KANE:
17 Q. Understood.
18 A. We want to get them out. We are not sure
19 that there's much benefit to going in and out in terms
20 of brain injury and longterm consequences.
21 Q. In the -- I guess in the short term would
22 you prefer to have them out rather than in status?
23 A. The problem is every time they go back in it
24 escalates therapy and increases risk. As we saw
25 elsewhere even in the Marinus document there's

1 significant cardiorespiratory risk in escalating these
2 anesthesia treatments.
3 Q. Handing you Exhibit 1009 which is the Zhang
4 publication. This is a document that you reviewed?
5 (Exhibit 1009 was marked for identification
6 by the Reporter.)
7 THE WITNESS: Yes.
8 BY MR. KANE:
9 Q. And if we look at -- and I think you
10 testified earlier that like the 817 patent Zhang does
11 not have any human data?
12 A. No.
13 Q. If you turn -- this is confusing --
14 paragraph 22. It's on either page 4 or 5 depending --
15 the bottom number is 5.
16 A. Yes.
17 Q. You see it describes here that a patient is
18 a human or nonhuman animal in need of treatment?
19 A. Yes, I see that.
20 Q. You see that? Are you aware of nonhumans
21 that are in need of treatment for SE?
22 A. We -- only when we give it to them in the
23 experimental setting. There may be in veterinarian
24 practice but that's outside my scope. But in my world
25 we use the term "patient" only for humans. And I'm a

1 basic scientist as well and in the laboratory we don't
2 call them patients.
3 Q. Right. But in this particular patent
4 describes a patient as a nonhuman; correct?
5 A. Yeah. They have chosen to but that's not
6 common usage.
7 Q. So I'm going to mark this one. It will be
8 1050.
9 (Exhibit 1050 was marked for identification
10 by the Reporter.)
11 BY MR. KANE:
12 Q. So I've handed you what's been marked as
13 Exhibit 1050, Dr. Sankar. So to your point this is a
14 document that I don't believe you've seen before. It's
15 called "Status Epilepticus and Cluster Seizures";
16 right?
17 A. Yes.
18 Q. And this is a veterinarian publication
19 relating to SE in dogs and cats. Do you see that?
20 A. Yes.
21 Q. So that's a nonhuman --
22 A. Yeah.
23 Q. -- animal that is subject to SE?
24 A. Yes.
25 Q. I'll mark 1051.

1 (Exhibit 1051 was marked for identification
2 by the Reporter.)
3 BY MR. KANE:
4 Q. So again, this is a document I don't believe
5 you've probably seen before; is that correct?
6 A. I have only very superficially looked at it.
7 It's veterinary.
8 Q. Have you seen this before today?
9 A. Not in detail, no.
10 Q. At any time?
11 A. No.
12 Q. So Exhibit 1051 is titled "ACVIM Consensus
13 Statement on the management of status epilepticus and
14 cluster seizures in dogs and cats"; correct?
15 A. Uh-huh.
16 Q. So this is describing veterinary treatment
17 for nonhuman animals that have SE?
18 A. Uh-huh.
19 Q. Is that yes?
20 A. Yes.
21 Q. So in Zhang when it refers to a nonhuman
22 patient that could be a dog or a cat?
23 A. In veterinary practice, yes. But not in
24 human practice.
25 Q. But in the Zhang patent it refers to a

1 patient as including nonhumans; correct?
2 A. Yes, that's how they defined it.
3 Q. Do you have the 817 patent in front of you?
4 A. Yes.
5 Q. So if you look at page 23, and if you look
6 at the right-hand column, column 32 at the very bottom
7 starting at line 65 see it says, "patient" and
8 "subject" are used interchangeably herein and include
9 but not limited to primates such as humans, canines,
10 porcine, ungulates, rodents, poultry and avian; right?
11 A. Yes.
12 Q. So in that patent they've also described
13 patient to include nonhuman; right?
14 A. Yes.
15 Q. But your opinions are all based on the idea
16 that the claims in the patent are limited to human?
17 MS. PEHRSON: Objection to the extent it
18 mischaracterizes his testimony. Vague.
19 THE WITNESS: The claims at the end of this?
20 BY MR. KANE:
21 Q. Yes.
22 A. I think they pertain to proposed human use.
23 Q. So they're limited to human use?
24 A. But the dosages are not consistent with some
25 other species.

1 Q. Why do you say that?
2 A. Doses in the range you would not be able to
3 administer to a rodent.
4 Q. Could you administer them to a dog?
5 A. Again, depends on the size of the dog.
6 Q. How about a porcine?
7 A. Again, it depends on the size. I would say
8 we're outside my realm of practice or even experiment.
9 Q. So you don't have any knowledge one way or
10 the other what dosage would be administered to canines?
11 A. No.
12 Q. You don't have any knowledge of what doses
13 would be administered to porcines?
14 A. No.
15 Q. And Dr. Sankar, looking at your CV it
16 appears as though you were involved in a clinical study
17 with Marinus involving ganaxolone and treatment of
18 patients with infantile spasms?
19 A. Yes, very long time ago.
20 Q. 2007 to 2009?
21 A. Yes.
22 Q. What was your experience there?
23 A. The only two patients I enrolled did not
24 benefit from it.
25 Q. And can you describe that study for me?

1 A. It was a study that had a lot of pitfalls in
2 the design but we are sometimes stuck with them. It's
3 a very difficult syndrome to treat to this day and the
4 patients who entered the study for ethical reasons and
5 IRB requirements had to have failed two of the most
6 prominent standard treatments. And so it ended up
7 filtering the patients who entered the study into
8 nearly impossible patients that have already been
9 failing all the standard things that work in many other
10 patients.
11 Q. Would the experience in that study have any
12 impact on your analysis of the use of ganaxolone for
13 treating SE?
14 A. No. But they're very different
15 circumstances patho-physiologically.
16 Q. How was the therapy delivered in that study?
17 A. By mouth.
18 Q. So orally rather than through IV?
19 A. We have never had IV product in this space.
20 Q. In what space?
21 A. When we did the infantile spasm study, but
22 even if we did we wouldn't have given it IV because
23 this is not an acute emergency but a seizure disorder
24 that requires treatment for months so you're not going
25 to be doing IVs. Everything used with the exception of

1 ACTH that's limited to two weeks is usually given by
2 mouth.
3 Q. I'll hand you what's been marked as Exhibit
4 1013, Dr. Sankar.
5 (Exhibit 1013 was marked for identification
6 by the Reporter.)
7 BY MR. KANE:
8 Q. If we look at the -- the first page is
9 pretty small print so it's hard to read, but page 2 has
10 kind of a blowup in the upper left-hand portion of the
11 poster, and you see in the first bullet there under
12 "Overview" it describes -- it calls it "convulsive
13 status epilepticus can be modeled in experimental
14 animals by administration of lithium and pilocarpine."
15 Do you see that?
16 A. Yes.
17 Q. I think that's what you described earlier
18 this morning?
19 A. Yes.
20 Q. And it continues to say that "Rats subjected
21 to experimental CSE are refractory to benzodiazepine if
22 treatment is initiated greater than 15 minutes after
23 seizure onset." Do you see that?
24 A. Yes.
25 Q. Is that consistent with your understanding?

1 A. That's generally true.
2 Q. And it continues to say, "thus modeling a
3 treatment resistant form of CSE." Do you agree with
4 that?
5 A. Yes.
6 Q. It says, "This treatment resistant form of
7 the disease is considered to be a clinically
8 translatable model of disease"; correct?
9 A. That's arguable.
10 Q. Why do you say that arguable?
11 A. Because none of the SE cases in humans with
12 the exception of insecticide poisoning will resemble a
13 cholinergic overstimulation. That's what the
14 insecticides do, organophosphates. That's kind of what
15 happens with pilocarpine. And we have used other
16 models as well. There are models where you don't use a
17 chemical at all but just put electrodes and stimulate
18 the hippocampus.
19 Q. What other models have you used besides the
20 pilocarpine model?
21 A. Continuous hippocampus stimulation model.
22 If you stimulate a rat in the strategic limbic circuit
23 sides even if you stop the stimulation electrically
24 after 30 minutes they'll keep going. So again, we call
25 it self-sustaining SE or SSSE.

1 So lithium pilocarpine is a way and it has
2 some downsides such as very high mortality and also the
3 pilocarpine you used is not gone in 15 -- it's still
4 very much there. So the provocation continues for a
5 good bit of time, as long as the pilocarpine is in the
6 system.
7 Q. When would you use the hippocampus versus
8 the pilocarpine model?
9 A. Depends on what you're trying to do. We
10 have used both. We've used kainic acid. There are
11 different models depending on what you want to study
12 for your particular project, what's an advantage versus
13 disadvantage.
14 Q. Is that a third model then?
15 A. That's also a model of status, yes.
16 Q. How does that model work?
17 A. It's a neurotoxic compound but it works on
18 a -- it's a glutamate-oriented thing rather than a
19 cholinergic thing.
20 Q. Once the status is created with any of these
21 models, is there any difference?
22 A. Well, there are some differences because I
23 think in all of them at some point they become what we
24 call self-sustaining, but the pilocarpine model you
25 still have that agent. In the kainic model there's

1 often injury to where you inject it in the hippocampus.
2 That's kind of driving it. The electrical is clean
3 chemically speaking but none of them simulate the human
4 condition because we're not under continuous electrical
5 stimulation as people.
6 Q. But as it turns out I guess both in the 817
7 patent and in the Zhang publication they used the
8 pilocarpine model?
9 A. Yes. It's a commonly used model. It's been
10 around a long time.
11 Q. Do you have any reason to believe that the
12 use of the pilocarpine model would not be appropriate
13 in studying ganaxolone?
14 MS. PEHRSON: Objection. Vague. Foundation.
15 THE WITNESS: I think their goal in this
16 particular case based on the understood pharmacology of
17 ganaxolone was specifically to find a model where they
18 can support that it's benzodiazepine resistant.
19 BY MR. KANE:
20 Q. And what was the importance of having a
21 benzodiazepine resistant model?
22 A. The benzodiazepine resistance comes from the
23 fact that synaptic GABA receptors are being
24 internalized, they're lacking access to them. So the
25 pharmacology of ganaxolone is to also act at the extra

1 synaptic GABA receptors that do not get internalized.
2 So they're kind of targeting at what you may say
3 enduring target which is not amenable to
4 benzodiazepines.
5 Q. I think you said earlier that you were
6 engaged to work on this in August?
7 A. Yes.
8 Q. And in terms of the drafting process for
9 your declaration, can you generally describe that
10 without getting into the substance?
11 MS. PEHRSON: Just caution you not to disclose
12 any substantive conversations you had with counsel.
13 THE WITNESS: It was developed with counsel. I
14 provided the scientific input. I'm not used to the
15 legalistic language drafting.
16 BY MR. KANE:
17 Q. So you provided the scientific input and
18 counsel did the drafting?
19 A. We worked collaboratively.
20 Q. Did you edit the document?
21 A. Before I signed it yes, and made some
22 changes.
23 Q. Do you have any idea how much time you spent
24 developing the declaration?
25 A. I did not time specifically for the

1 declaration but I spent a lot of time going over a
2 number of these posters and things we have here to
3 familiarize with the issues.
4 Q. What's the total time that you spent before
5 you signed the declaration? Do you have any idea?
6 A. Probably in the neighborhood of 20 to 25
7 hours.
8 Q. And did you do some work to prepare for your
9 deposition here today?
10 A. Merely kind of reviewed the typical rules
11 for deposition.
12 Q. And did you meet with counsel?
13 A. Yes.
14 Q. And when did you meet?
15 A. Yesterday.
16 Q. And how long was the meeting?
17 A. Probably four to five hours.
18 Q. Did you do anything else to prepare for the
19 deposition?
20 A. We reviewed some of the patent and the
21 contesting literature.
22 Q. But I mean before yesterday did you do any
23 work to prepare?
24 A. For the deposition?
25 Q. Yes.

A. No.
Q. Did you talk to anybody other than counsel?
A. No.
MR. KANE: I think I have no further questions at this time.
MS. PEHRSON: I have no questions. I did want to put one objection on the record, that the petitioner has not yet filed a notice of deposition for Dr. Sankar.
And I need a copy of the transcript.
(Ending time 1:40 p.m.)

1 STATE OF CALIFORNIA)
2)
3 COUNTY OF LOS ANGELES)
4
5 I, RAMAN SANKAR, M.D. PH.D, hereby certify under
6 penalty of perjury under the laws of the State of
7 California that the foregoing is true and correct.
8 Executed this _____day of
9 _____, 2024 at
10 _____, California.
11
12
13 _____
14 RAMAN SANKAR, M.D. PH.D
15
16
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REPORTER'S CERTIFICATE

I, JEANINE CURCIONE, C.S.R. NO. 10223, RPR, in and for the State of California, do hereby certify:

That prior to being examined, the witness named in the foregoing deposition was by me duly sworn to testify the truth, the whole truth and nothing but the truth and that the witness reserved the right of signature;

That said deposition was taken down by me in shorthand at the time and place therein named, and thereafter reduced to typewriting under my direction, and the same is a true, correct and complete transcript of said proceedings.

I further certify that I am not interested in the event of the action.

Witness my hand this 15th day of February, 2024.

Certified Shorthand
Reporter for the
State of California

DEPOSITION ERRATA

Deposition of: Raman Sankar, M.D., Ph.D.
Date of Deposition: February 9, 2024
Case: No. PGR2023-00020
U.S. Patent No. 11,395,817

Page	Line	Transcript Text	Correction	Reason
7	5	physiology pharmacology	physiology and pharmacology	Transcription error
8	7	transitional complex	the transition of complex	Transcription error
10	8	clinic	clinical	Transcription error
11	8	science whether it fits	science and whether it fits	Transcription error
12	11-12	Well, the subset of them generally medications	Well, a subset of them – generally medications	Transcription error
16	15-16	medication is	medications	Transcription error
17	12-13	So seizures can become the term use is self sustaining	So seizures can become, the term used is self-sustaining,	Transcription error
32	15	How many of them.	How many of them survive.	Misspoke
38	16	backouts	plateaus	Transcription error

I, Raman Sankar, do hereby certify that I have read my deposition transcript dated February 9, 2024; that the changes and corrections to my deposition transcript set forth above are necessary to render the same true and correct; that having made such changes, I hereby subscribe my name to the deposition. I declare under penalty of perjury that the foregoing is true and correct.

Executed this 5th day of March, 2024.

R. Sankar

Digitally signed by Raman Sankar, MD, PhD
DN: cn=Raman Sankar, MD, PhD, o=UCLA, ou=Pediatric Neurology, email=RSankar@ucla.edu, c=US
Date: 2024.03.05 11:03:59 -08'00'

Raman Sankar