UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

INSYS DEVELOPMENT COMPANY, INC.,
Petitioner,
vs.
GW PHARMA LIMITED,
Patent Owner.

Petition for Inter Partes Review of U.S. Patent No. 9,066,920

DEPOSITION OF:
LESLIE BENET, PH.D.
October 5, 2017
9:03 a.m.

500 West Madison Street
Chicago, Illinois

Reported By:
Deanna Amore,
CSR, RPR, 084-003999
Job No. 2685666

Pages 1 - 52

Page 1

APPEARANCES OF COUNSEL

On Behalf of the Petitioner, INSYS DEVELOPMENT COMPANY, INC.:

WOOD, PHILLIPS, KATZ, CLARK & MORTIMER
MR. DEAN A. MONCO
MR. STEVEN F. WEINSTOCK
MR. MARK V. POLYAKOV
500 West Madison Street
Suite 1130
Chicago, Illinois 60661
(312) 876-2110
sfweinstock@woodphillips.com
mpolyakov@woodphillips.com
damonko@woodphillips.com

On Behalf of the Patent Owner, GW PHARMA LIMITED:

FISH & RICHARDSON
MS. MARTINA TYREUS HUFNAL
222 Delaware Avenue
17th Floor
Wilmington, Delaware 19801
(302) 778-8471
hufnal@fr.com

- and -

FISH & RICHARDSON
MS. DOROTHY P. WHELAN
3200 RBC Plaza
60 South Sixth Street
Minneapolis, Minnesota 55402
(612) 337-5209
whelan@fr.com

ALSO PRESENT:

Marie Aucoin, Ph.D., JD
Insys Therapeutics, Inc.

I N D E X

EXHIBITS

(Whereupon, the witness was duly sworn.)

MS. HUFNAL: Good morning, Dr. Benet.

THE WITNESS: Good morning.

LESLIE BENET, PH.D.,

called as a witness herein, having been first duly sworn, was examined and testified as follows:

CROSS-EXAMINATION

BY MS. HUFNAL:

Q. Have you been deposed before? 09:03:49

A. Yes.

Q. How many times?

A. Somewhere north of 50.

Q. Have any of those depositions been in the context of a patent litigation?

A. Most of them.

Q. Have you been serving as an expert in those depositions?

A. Yes.

Q. Have you ever testified before in an IPR proceeding? 09:04:01

A. Not in the U.S. In Germany -- well, different, yeah.

Q. Different type of proceeding?

A. Right. Yes.

Q. In those depositions where you're testifying as an expert, can you give me a high-level description of what you were testifying as an expert in?

A. It's always validity of patents or obviousness or...

Q. Have you been testifying as a pharmacokinetics or --

A. Yeah. Drug development, pharmacokinetics, pharmacodynamics, biopharmaceutics. 09:04:46

Q. Have any of those engagements been on behalf of Inysis before this one?

A. No.

Q. I am going to go over a few ground rules. You have been deposed before, but I'll do it for the sake of procedure here. Okay?

A. Okay.

Q. I am going to be asking you questions today, and you are going to be giving me answers. You understand that? 09:05:14

A. I do.

Q. And since the court reporter is taking everything down, we should try to speak independently of each other. So let me finish my question before you answer. Is that okay?

A. I will try.
Q. I will need verbal answers so the court reporter can take it down. Do you understand that?
A. I recognize that.
Q. If I ask a question that you do not understand at any point, will you please let me know?
A. I will.
Q. And if you answer my question, I'm going to assume that you have understood it. Is that fair? 09:05:37
A. That's fair.
Q. You understand that you are under oath today, correct?
A. I do.
Q. It's the same oath as if you were in a courtroom in the United States; do you understand that?
A. I do.
Q. Is there any reason, medical or otherwise, why you are not able to give accurate and truthful testimony today? 09:05:51
A. No reason.
Q. Dr. Benet, you have a Ph.D. in pharmaceutical chemistry; is that right?

A. That's correct.

Q. You are also a professor at the School of Pharmacy at UCSF?

A. That's correct.

Q. What do you teach at UCSF?

A. Pharmacokinetics, drug metabolism, drug transporters, pharmacodynamics are my areas of specialty.

Q. I'm going to give you the declaration that you have submitted in this proceeding so you can refer to it at any point. I'm handing you what's been previously marked as Inysis Exhibit 1003. 09:06:27

Dr. Benet, does Inysis Exhibit 1003 appear to be the expert declaration that you submitted in this IPR proceeding? I think along with your CV?

A. Oh, wow. Got my more recent publications.

Yes.

Q. And so just so the record is clear Exhibit 1003, up to page 11, is that the substance of the declaration you have submitted in this proceeding? 09:07:30

A. It is.

Q. And starting on page 12 of the exhibit onward is the detailed curriculum vitae of you, right?

A. It looks like it is, yes.

Q. If we could stick, actually, on page 12 of Exhibit 1003, your CV, you have -- paragraph 4 states your areas of specialization; do you see that?

A. Yes.

Q. And are those the areas in which you are testifying as an expert here today and in this proceeding?

A. Yes. Primarily pharmacodynamics in this proceeding. 09:08:08

Q. Pharmacodynamics?

A. Uh-huh.

Q. Can you explain to me what pharmacodynamics is?

A. Pharmacodynamics is what a drug does to a patient. Pharmacokinetics is what a patient does to a drug.

Q. Starting with pharmacodynamics, is that a study of the impact -- the physiologic impact of a drug on a patient? 09:08:49

A. Well, outcome -- giving a drug to a patient and understanding the outcomes of efficacy, toxicity and the model that you use to evaluate it. But it's not just patients. It's models and

animals you could use also in predicting what's going to happen.

Q. And pharmacokinetics, you say what a patient does to the drug. Is that then, in other words, how the drug is broken down in the body or what happens to the drug in the body?

A. Yes. How it gets in, how it gets out, how the body controls it or tries to control it.

Q. Dr. Benet, you are not a clinician, right?

A. I am not a -- well, what do you mean by "clinician"? 09:09:35

Q. Have you ever treated patients?

A. What do you mean by "treated patients"? Do I actually see patients and make drug dosing decisions? No.

Q. Have you ever treated a patient with seizures or epilepsy?

A. No.

Q. In your work have you worked on antiseizure drugs? 09:10:00

A. Yes.

Q. How many?

A. How many drugs?

Q. Antiseizure drugs.

A. Well, my last paper last year, there were

probably 15 drugs in it.

Q. Have you, yourself, done research on those antiseizure drugs?

A. Well, "do research."

I direct research on antiseizure drugs, yes. Do I do research myself? No. I drink coffee.

Q. Do you consider yourself an expert in seizures or epilepsy?

A. No, I do not. 09:10:39

Q. We're going to be discussing the MES model.

A. Correct.

Q. Have you ever run an MES study?

A. No.

Q. Have you ever used the MES model?

A. "Used" means physically used? What do you mean by "used"?

Q. Yes, physically used.

A. No. 09:11:01

Q. Have you ever seen one run?

A. No -- yes, I have. I have seen one run.

Q. Have you published on the MES model?

A. No.

Q. Have you used other antiseizure models

other than the MES model in your research?
A. For efficacy or for what?
Q. For efficacy.
A. No.
Q. Have you published on any antiseizure models other than the MES model?
A. Yes, but not efficacy model.
Q. Okay. What type of models?
A. Toxicity models.
Q. The MES model is an efficacy model, right? 09:12:01
A. Yes.
Q. Dr. Benet, have you ever worked on CBD?
A. Yes.
Q. Have you published on CBD?
A. Yes.
Q. How many publications?
A. Five.
Q. Can you give me rough years on when those publications came out?
A. '80s and '90s. Probably -- yeah, more likely '90s. 09:12:34
Q. What were you studying about CBD in those publications?
A. How it's eliminated from the body and how it can potentially interact with other drugs.

Q. Was any of that work related to the efficacy of CBD on any particular disease or ailment?

A. Well, it was related to what potential user toxicity issues that could result from this kind of interaction.

Q. Right.

So I just want to understand your work with CBD. Other than looking at the potential toxicity issues of CBD, were you studying whether or not it was efficacious against any treatment? 09:13:21

A. No.

Q. Have you ever run any PK or PD studies on CBD?

A. Yes.

Q. Have you published those studies?

A. Yes.

Q. Are you a named author on those papers?

A. Yes.

Q. You didn't rely on any of those papers for purposes of this declaration, did you? 09:13:57

A. No.

Q. So let's look at your declaration, Exhibit 1003.

This document contains all of the opinions

and the bases for those opinions that you provided in this proceeding, fair?

A. Yes.

Q. Now, you also submitted a declaration in a European proceeding between Inysis and Greenwich, correct?

A. Yes.

Q. And that declaration is substantially similar to the declaration you submitted here?

A. They are similar. 09:14:44

Q. How many hours would you say you spent working on those two declarations?

MR. MONCO: Together?

MS. HUFNAL: Together.

THE WITNESS: 23.

BY MS. HUFNAL:

Q. I'm sorry. Does it say that in here?

A. No.

Q. Oh, okay. 23 hours?

A. Yes. 09:14:58

Q. You just pointed to your declaration, so I thought I had missed it in here.

A. No. I was just answering your question.

Q. And I do believe in here you state that your hourly rate in this matter is $750 per hour;

is that right?

A. Yes. For the report, yes.

Q. Is it different for the deposition?

A. Yes.

Q. What is it for the deposition?

A. $1,500 an hour.

Q. Did you prepare for the deposition today?

A. I did.

Q. What did you do to prepare?

A. I read my expert report and some of the references, and yesterday I met with the attorneys from Wood Phillips to prepare for today. 09:15:33

Q. How long would you say you spent preparing for the deposition?

A. Independently, three hours, and with them yesterday, seven hours.

Q. Is that preparation for the deposition at the same rate, $1,500 an hour?

A. It is.

Q. I'd like to look, if we could, at your declaration, Exhibit 1003, on page 2. At the bottom of page 2, there is a section called "Materials Considered"; do you see that? 09:16:07

A. I do.

Q. And paragraph 8 states "The list of

materials I considered in setting forth the declaration in this matter includes," colon, and it has a list of papers; do you see that?

A. I do.

Q. Is that the entirety of the list of documents that you considered in forming your opinions in this case?

A. No. I read at least 30 or 40 other papers.

Q. For -- why didn't you include them in this list? 09:16:53

A. Well, because I didn't rely on them.

Q. These materials here listed under paragraph 8 are the documents that you relied on in setting forth your opinions in this case, right?

A. Right.

Q. Okay. And those include -- I am just going to make sure I understand this list here -- the '920 patent? Is that one?

A. Yes. 09:17:20

Q. The Cunha reference?

A. Yes.

Q. An office action dated August 25, 2015?

A. Yes.

Q. The WO '109 patent application?

A. Yes.
Q. A Mechoulam paper?
A. Yes.
Q. Pertwee book chapter?
A. Yes.
Q. Malfait?
A. Yes.
Q. Lindamood paper?
A. Yes.
Q. Zuardi paper? 09:17:50
A. Yes.
Q. Consroe and Wolkin paper?
A. Yes.
Q. Wallace paper?
A. Yes.
Q. And a Castel-Branco paper?
A. Yes.
Q. I got the complete list there, right?
A. You do.
Q. You did not rely on, for purposes of your 09:18:05
declaration, a paper authored -- first author Ames, did you?
A. Did I rely on it?
I didn't reference it, but I'm well aware of it.

Q. You didn't rely on it for purposes of your expert opinion in your declaration, correct?
A. I didn't reference it.
Q. Well, and you understand the purpose of submitting an expert report like this is so that we have fair notice of your opinions and the bases for those opinions? Do you understand that?
A. Yes.
Q. Okay. So in your declaration you did not cite to and, therefore, rely on the Ames paper, correct? 09:18:40
A. I did not cite it.
Q. And the same is true for the Bhattacharyya paper?
A. Bhattacharyya, right.
Q. You did not list that in the materials in your declaration, right?
A. I believe I did not.
Q. And you did not include, in your list of materials considered in forming your opinions, a declaration of Dr. Marson, correct? 09:19:08
A. Correct.
Q. If we flip over to just the next page, page 3 of Exhibit 1003, under the "Legal Standards," paragraph 9, you set forth a definition

for a person having ordinary skill in the art; do you see that?

A. I do.

Q. And you set forth your definition of a person of ordinary skill in the art in that paragraph; is that correct?

A. Yes.

Q. And you state "A person of ordinary skill in the art would typically have an MD, Ph.D. or equivalent in pharmacology, chemistry, biochemistry, neurology or in a related field in the biological or chemical sciences"; do you see that? 09:19:56

A. Yes, I do.

Q. And you agree with that definition?

A. Yes.

Q. Now, the Greenwich patent that we're talking about, the '920 patent, do you understand that that is directed to the treatment of partial seizures using CBD generally? 09:20:23

A. I mean, it says more than that, yes.

Q. Well, for purposes of your person of ordinary skill in the art, your definition doesn't require any knowledge or experience with seizures, correct?

A. That's correct. My definition says you are a scientist; you know how to do pharmacology. You know how to read the literature; you know how to make decisions whether studies are valid or invalid.

Q. Okay. But your definition of a person of ordinary skill in this art does not require any knowledge of or experience with seizures, correct?

A. That's correct.

Q. Okay. And your definition of person of ordinary skill in the art, of this art, also doesn't require any knowledge or experience with CBD, correct? 09:20:56

A. That's correct.

Q. Let's go to paragraph -- the next page, page 4. Section D is titled "Prior Art Suggests Daily Dose of at Least 400 milligrams CBD for Treatment of Partial Seizures"; do you see that?

A. Yes.

Q. And the first subsection is titled "Higher Doses of CBD were Suggested in the Prior Art," right? 09:21:45

A. Yes.

Q. Is this where, in your declaration, you discuss the clinical data or publications involving

CBD for treating seizures?

MR. MONCO: Objection. Vague.

THE WITNESS: Well, I mean, no, because I reference all of these papers that review all of this data, Pertwee and Zuardi. So this doesn't limit it.

BY MS. HUFNAL:

Q. Sure.

So under this section "Higher Doses of CBD Were Successful in the Prior Art," you specifically cite to two papers, Cunha and Zuardi, correct? 09:22:31

A. Correct.

Q. And both of those papers are reporting on a clinical study, fair?

A. I'm not sure Zuardi was a clinical study. I mean, this was a study in humans, but I'm not sure. I don't know how you are using "clinical."

Q. Great point.

So Zuardi related to safety, not efficacy, correct? 09:23:07

A. Correct.

Q. So, of those two, the only paper that reports on the clinical efficacy in humans for CBD is Cunha, right?

A. Of these two, is that what you're saying? Is that your question?

Of the two papers listed here, Cunha is the one paper that talks about clinical study in humans, yes.

Q. And you don't cite anywhere else in here a paper that is studying a clinical efficacy study of CBD, do you?

A. Well, I cite Pertwee, and he reviews all of it. 09:23:48

Q. Okay. But Pertwee -- I certainly want to talk about Pertwee.

In terms of papers that are publishing on clinical -- a discrete clinical study of the efficacy of CBD, Cunha is the one you have in your declaration, correct?

A. That's correct.

Q. And just so I'm clear, Cunha, in the efficacy portion of the Cunha study, the maximum dose used to treat seizures of CBD was 09:24:17 300 milligrams, correct?

A. Correct.

Q. So let's look at Zuardi. I would like to look at Zuardi with you. It's Exhibit 1025. I'll hand you that document.

Do you recall reviewing the Zuardi paper, Exhibit 1025?

A. I do.

Q. Is this one of the documents you reviewed in preparation for your deposition yesterday or leading up to this deposition?

A. I actually did not read this paper yesterday.

Q. I want to give you the time that you need to review and to answer my questions. That's why I was asking if it happened to be fresh in your mind. 09:25:28

A. Okay.

Q. Let's turn to page 272 of Zuardi, Exhibit 1025.

And do you see a section in the right-hand column, "No. 1. Antiepileptic Action"?

A. Yes.

Q. And there is a paragraph here in Zuardi that's discussing -- kind of summarizing the antiepileptic action of CBD that was known; is that fair? 09:26:14

A. Yes.

Q. And you should feel free to read it, if you want. My question is there is a discussion here about a double-blind study, and it summarizes

the results, and it's followed by Footnote 38.

And so my question is is that discussion in Zuardi that is supported by Footnote 38 the same Cunha study that you cite in your declaration?

A. Yes. But he also references Ames. So...

Q. That was going to be my next question.

So after the discussion of Cunha, the next sentence "In a less successful study, no significant improvement in seizure frequency was observed among 12 epilepsy patients who received 200 or 300 milligrams of cannabidiol per day in addition to standard epileptic drugs"; do you see that? 09:27:09

A. I do.

Q. And the footnote there is to Reference 39, and that's the Ames paper?

A. Yes.

Q. You did not rely on the Ames paper in your declaration for your opinions, right?

A. I did not cite the Ames paper. I mean, Ames said he should try higher doses, but he couldn't. 09:27:30

Q. You did not cite the Ames paper in your declaration, did you?

A. That's correct.

Q. The Zuardi paper that you did cite concludes this section on antiepileptic action stating "Therefore, the clinical efficacy of CBD on epilepsy is still uncertain"; do you see that?

A. Yes.

Q. Now, you cite to page 274 of the Zuardi paper; is that correct?

A. Well, I cite 1500 milligrams.

Q. I do not want to be misleading you. So in paragraph 13 of your declaration it says "Zuardi at page 274"? 09:28:21

A. Right.

Q. I just want to make sure that I understand what you are relying on. Are you then citing to the discussion in the first full paragraph on the left-hand column of 274 in Zuardi?

A. Correct.

Q. And that is a study in schizophrenic patients; is that right?

A. Right. 09:28:43

Q. Receiving oral doses of CBD?

A. Correct.

Q. The studies there that you are relying on were evaluating the efficacy of CBD as an antipsychotic; is that correct?

A. Correct.
Q. They were not studying the efficacy on epilepsy, right?
A. They were not.
Q. And they weren't studies that were performed in seizure patients, right?
A. They were just looking at safety.
Q. I just want to make sure we are on the same page. The studies that you are relying on here in Zuardi were not studies that were done on seizure patients, correct? 09:29:15
A. It was a schizophrenic patient.
Q. And that's not a seizure patient, correct?
A. Right.
Q. Okay. So we can go back to your declaration. Something I should have said at the beginning, Dr. Benet, if you need a break at any point, please just let me know.
A. Thank you.
Q. So let's go back to your declaration, paragraphs 4 and 5. 09:29:42
The next section "Higher Doses of CBD Would be Likely to Increase CBD Effects"; do you see that?
A. I do.

Q. Your opinion in this section of your declaration is based on the assumption that CBD for seizures has a sigmoidal dose response curve; is that fair?

A. It's based on that all of the data and the literature says that it is.

Q. Right. I just want to understand the underlying assumptions to your opinions in this case.

And one of the assumptions that is the basis for your opinions is that CBD has a sigmoidal dose response curve, correct? 09:30:29

A. It's not an assumption. It's based on the data and the literature that shows that there is no data that shows that that's not true.

Q. So your opinions, though, in this -- and I don't mean to characterize your analysis as an assumption -- but your opinion in this case is based on your understanding that the dose response curve for CBD for seizures is sigmoidal in shape, correct? 09:30:58

MR. MONCO: Objection. Asked and answered.

THE WITNESS: Correct.

BY MS. HUFNAL:

Q. As opposed to a bell-shaped curve, right?

A. That's correct.
Q. Now to reach the conclusion that CBD for seizures has a sigmoidal dose response curve, you rely on, I think, but correct me if I'm wrong, two references, Lindamood and Wallace?
A. I cite two references, Lindamood and Wallace.
Q. Okay. And that's all I have to go off of. So you cite to two references, Lindamood and Wallace, for your conclusion that CBD for seizures has a sigmoidal dose response curve, correct? 09:31:41
A. No. Pertwee does 16 different studies that show a sigmoidal dose response curve.
Q. So it's your understanding that there are 16 studies in Pertwee that show a sigmoidal dose response curve?
A. Right.
Q. Did you include that analysis, showing the sigmoidal dose response curve, in your declaration?
A. I was giving examples, Lindamood and Wallace, one in mice and one in rats. 09:32:08
Q. And, actually, in this section here of your declaration, subheading (b), "Higher Doses of CBD would be Likely to Increase CBD Effects," paragraph 14 through 23, you don't cite to Pertwee

in any of those paragraphs, right?

A. Paragraph 23, 20, 22. I don't list Pertwee, but it's fairly obvious. The literature has clearly shown according a skilled person familiar with the literature. The literature isn't Lindamood and Wallace.

Q. Okay. So other than Pertwee, Lindamood and Wallace, what other references, in your opinion, even though not included in your declaration, do you think support the conclusion that CBD has a sigmoidal dose response curve for seizures? 09:33:05

A. The 16 studies cited by Pertwee.

Q. So let me focus on the two that you actually cite in your declaration, Lindamood and Wallace. Those were both studies done in the MES model, correct?

A. Correct.

Q. Now, you state in paragraph 16 that the "MES model is currently the best available model for identifying and testing anticonvulsant compounds, i.e., drugs that treat seizures"; do you see that? 09:33:42

A. Referring to Castel-Branco, quoting him -- him -- her.

Q. So your support for that conclusion is Castel-Branco?
A. Correct.
Q. Let's look at Castel-Branco. It's a document previously marked as Exhibit 1028.
Is this one of the documents you have recently reviewed?
A. I have.
By the way, it's -- in my declaration, the "L" in Castel is missing in paragraph 16. 09:34:44
Q. Okay. If you look at -- well, first, Castel-Branco is not reporting on partial seizures specifically, is it?
A. Well, the paragraph I quote, no.
Q. If you go to the first page of Exhibit 1028 under the "MES Test" heading, do you see that?
A. Yes.
Q. And here it says that "The MES test is probably the best validated preclinical test that 09:36:15 predicts drugs effective against generalized seizures"; do you see that?
A. I do.
Q. Do you agree with that?
A. Yes.

Q. Castel-Branco in -- well, let me just ask you instead of pointing you directly to sentences.

Would you agree that Castel-Branco describes the MES model as useful in early stages of testing?

A. Correct.

Q. And the MES model is a screening tool for antiseizure drugs?

A. Correct.

Q. And Castel-Branco does reference partial seizures on page 5 of Exhibit 1028 and states that "The MES model can actually fail to identify drugs that are clinically effective against partial seizures." Do you agree? 09:36:53

A. Do you want to give me the page?

Oh, 5, I see. 5 and 6.

Q. Absolutely.

A. I see it.

Q. Do you agree that the MES test can fail to identify drugs effective in treating partial seizures? 09:37:35

A. I agree with that statement, yes.

Q. Okay.

A. But there -- actually, you know, pilocarpine doesn't do it either, and penicillin

doesn't do it either.

Q. Those are other models used to test drugs for antiseizure activity?

A. Those are the models in the patent.

Q. The MES model -- Castel-Branco goes on to say -- "It does not distinguish between efficacy in the treatment of primarily and secondarily generalized tonic-clonic seizures"; do you see that?

A. Yes. 09:38:14

Q. Do you agree with that?

A. Well, most of the models do not distinguish. In reviewing the literature it's hard to see any model that does a really good job of distinguishing.

Q. Distinguishing between partial and generalized seizures?

A. Right.

Q. So I want to go back to the MES model and your -- another statement you made in the 09:38:38 declaration about that, if we could.

So if you go back to Exhibit 1003, page 5, specifically paragraph 17, you state in your opinion "MES is the best model for evaluating drugs for partial seizures"?

A. Right.

So if you had asked me in the beginning do I want to change anything in my declaration, I would have said I wanted to supplement that paragraph for saying "evaluating drug dosage for partial seizure."

Q. So is it now your opinion that the MES model is not the best model for evaluating drugs for partial seizures?

MR. MONCO: Objection. Mischaracterizes his testimony. 09:39:40

BY MS. HUFNAL:

Q. I just want to understand the --

A. I should have said -- no, I don't say that.

I just said what I should have said was that it's the "best model for evaluating drug dosage" because, as I just told you, I don't think any of the models do a good job of separating out the different -- the models do a good job of separating out the different -- partial versus the generalized. 09:39:57

Q. So it's your opinion that the MES model is the best model for evaluating drug dosage for partial seizures. Did I get that right?

A. Correct.
Q. What is your basis for that opinion?
A. That all of the studies that are there in the animal models don't show any difference between the various models for the drug doses from the MES model. When a drug is positive in partial seizures, you get the same dose response in the other models that you get for the MES model for the drug dosage.
Q. See if I can break that down. 09:40:57
You said when a drug is positive in the MES model?
A. Yes.
Q. Then what?
A. The dose that you would get from the MES model is the same as a dose, for example, in the Kindle model, as you would -- potentially could do a better job in getting the partial seizure drugs.
Q. So we haven't talked about the Kindle model yet. 09:41:36
A. And I never mention it in my expert report.
Q. You never mention the Kindle model in your declaration, right?
A. Yes.

Q. Did you just say that could potentially identify drugs for partial seizures better than the MES model?

A. According to Loscher and Bialer, it does because it -- for the Castel-Branco drugs that are listed that MES doesn't say are effective, the Kindle model appears to say they are.

Q. So why -- I'm not trying to be obtuse. I want to understand why do you think that the MES model is better -- well, is the best model for evaluating drug dose as opposed to any other model? 09:42:27

A. Right. Because it's simple, easy to do, and you can get the dose from it, and it doesn't show any differences in dosage from the other models.

Q. So when you say "it doesn't show any difference in dosage from the other models," are you referring to, like, the data in Pertwee, for example?

A. The animal study. 09:43:07

Q. The animal study.

A. Right.

But there is not a lot in Pertwee about the Kindle data.

Q. Okay. I don't want to get to the Kindle

yet. I want to understand the basis for the MES model as best I can.

So you went and looked at the dosage amounts reported for the MES models and then compared them to the other dosage amounts in the other studies to conclude that the MES model dosage was consistent?

A. Yes.

Q. And the reason that you think the MES model was the one to start with or the one to look at is because it's simple and easy to do? 09:43:54

A. Yeah, and reproducible.

Q. Are there any other reasons other than simple, easy to do and reproducible that you started with the MES model to compare it to the dosage in the other models?

A. Well, that's where most of the data in animals is, is in the MES model.

Q. Are there any other reasons?

A. Those are the ones I can think of now. 09:44:30

Q. So let me ask you, you cite to, in paragraph 21 of your report, a sentence in Wallace that says "The MES model is a model of partial seizures with secondary generalization"; do you see that?

A. I do.
Q. Do you agree with that?
A. I'm citing that because a POSA would read that and have no reason to think it was wrong, and so I don't actually know that that's true.
Q. You don't know one way or the other if that were true?
A. Well, as I said, all of these models show contradictory results depending on what study you look at. 09:45:36
Q. Let's go to a document that you have referenced now a few times, the Pertwee paper. It's Exhibit 1022.
A. Okay.
Q. I'll hand you that document. I think we already established that there were models other than the MES model to test the efficacy of drugs against placebo in 2009, right?
A. Yes.
Q. And you mentioned that you didn't discuss 09:47:06 the Kindle model in your declaration. Other than the MES model, you didn't discuss any other models in your declaration for treating efficacy in seizures, correct?
A. Right.

And the reason being that I can't see any differentiation between the pilocarpine and the penicillin in the patent and the MES models.

Q. You mentioned those a few times.

Have you, yourself, used either of those two models in the '920 patent?

A. I haven't used any of the models.

Q. By 2009 in the MES model there were reports of CBD not showing any activity against seizures, correct? 09:48:10

A. One paper.

Q. And that one paper is one of the papers that's listed in Pertwee, correct?

A. Reference 125.

Q. And Reference 125 is one of the references in Table 6 of Pertwee, correct?

A. Yes.

Q. In your declaration you didn't engage in any discussion about Table 6 of the Pertwee reference, correct? 09:48:38

A. I did not.

Q. On Table 6 there are three other references cited under the seizures induced by passing maximal electric shock currents through a corneal electrode model?

A. That's correct. But they are also listed as positive models in Table 4.
Q. So they are listed under both?
A. They are listed under both.
Q. So Pertwee is reporting on the same studies as having both no activity --
A. No. Different hertz. 6 hertz is the positive. 60 hertz is the negative. But it's the same study.
Q. Fair enough. 09:49:43
So portions of the same study show no activity and portions show some activity, correct?
A. Correct.
Q. And in Table 6 there are eight different seizures or behavior models listed?
A. Yes.
Q. If we look at Table 4 of Pertwee, there are also eight behavior models listed in Table 4, correct?
A. Correct. 09:50:32
Q. Are they the same behavior models listed on both?
A. Not exactly but there is a lot of overlap.
Q. So according to Pertwee, in several behavior models there was reported activity of CBD

against seizures and reports of inactivity of CBD against seizures?

A. Yeah, but the same paper. For example, look at Kindle. Look at Reference 11. It is listed as a positive in Table 4. It's listed as a negative in Table 6. So it's the same study, same paper, list, and this frequently -- if you go and look at the individual references, most of them are listed both places because it depends on what their pharmacodynamic measure is and whether they want to make a decision of whether yes or no. But the same papers will show positive effects for the same model as showing negative effects for the same model depending on what they measure. 09:51:23

So, I mean, the reason I don't reference any of these in my expert report is I haven't seen Dr. Whalley's response or rebuttal to me where he says I cherry-picked from these. Of course, I didn't cherry pick. There is 16 positive references for MES and 1 negative reference for MES. 09:51:58

Q. I'm not trying to characterize your opinion. I simply want to understand it here today. Okay?

And I think we are in agreement that there

is both positive and negative results for CBD against seizure as reported in the literature in different models, correct?

A. That's correct.

Q. Including the MES model, correct?

A. Correct.

Q. And for purposes of your declaration here, you looked at -- and here we have Lindamood is Reference 63, and I think Wallace is Reference 113. Do you understand that? 09:52:49

A. Right.

Q. Those are two of the references that are listed under the Behavior Model 1 in Table 4, correct?

A. That's correct.

Q. And there aren't any other behavior models in Table 4 that you discussed or considered in your declaration, fair?

A. No. No. Considered in my declaration. I considered all of these. What I discussed were 09:53:10 Lindamood and Wallace. I reference Pertwee, and I say "literature."

Q. Sure.

And in paragraph 8 of your expert report, it's "The list of materials I considered in forming

the opinions set forth in this declaration."

A. Which is Pertwee.

Q. Correct. But I'm trying to talk about the references -- the studies that are identified as references in Pertwee.

A. Correct.

Q. So I think you also, to be fair to you -- because I'm not trying to trick you -- Consroe is also one of the references in the Pertwee Table 4?

A. Correct. 09:53:52

Q. So other than Consroe, Lindamood and Wallace, you did not list in your "Materials Considered" any of the other references that are identified in the Pertwee Table 4?

A. Correct. I said "literature."

Q. And you did not list in your "Materials Considered" for this declaration -- I think it's any of the references in Table 6 of Pertwee, right?

A. No. Because the only references are the three that you mentioned that I particularly 09:54:31 discuss, yes.

Q. And none of those three -- I'm checking myself right now -- but none of those three are listed in Table 6 of Pertwee?

A. I'll look.

Can you help me with the reference number to Consroe?

Q. I absolutely can. I just lost my page.

So I believe it's 98, 63 and --

A. So Consroe is 98 then?

Q. Yes.

Let's make this record clear so when we're trying to go back and read it we will all know what we're talking about.

In Table 4 of Pertwee, Reference 98 is the Consroe reference that you discuss in your declaration, correct? 09:55:18

A. Yes.

Q. And Reference 63 is the Lindamood reference you talk about in your declaration?

A. Correct.

Q. And Reference 113 is the Wallace reference that you talk about in your declaration, correct?

A. It is.

And I did not specifically mention any of the Table 6 but -- okay. Yeah. 09:55:43

MS. HUFNAL: We are almost an hour. Let's take a short ten-minute break.

(A short break was taken.)

MS. HUFNAL: We have no further questions.

MR. MONCO: Okay. We'll take a break.

(A short break was taken.)

DIRECT EXAMINATION

BY MR. MONCO:

Q. Dr. Benet, what qualifies you to be an expert with regard to the subject matter of the '920 patent?

A. So as it says in my background and information, I'm chair of the pharmacology study section at NIH. I served as editor of journals. 10:34:29
I review for journals. Basically, I'm an expert scientist in the area of pharmacology, and I review all kinds of data of which I have no personal experience with.

I know how to look at data. I know how to analyze experiments. I know how to test whether something is valid or not valid and whether the interpretation has been correct. And this is what I do every day.

Q. As part of the duties that you just 10:34:57
identified, in your experience, have you done what is called or referred to as peer review of documents submitted for publication with regard to various drugs?

A. Correct. I do that -- I probably review

25 papers a year in peer review in terms of papers for the scientific literature.

Q. As part of your review, do you attempt to reproduce the experiments that are disclosed in the papers you review?

A. No.

Q. How do you conduct your review?

A. On the basis of good scientific procedures, whether they've been followed; whether there was a valid methodology; whether they've analyzed the data correctly; how they have used the prior literature; and whether they've been biased in terms of their interpretation. 10:35:41

That's the kind of information that I use to make my decision in terms of whether a paper is valid and whether the conclusions are valid.

Q. Do you recall your testimony with, I think you referenced, correct me if I'm wrong, I think you referenced Examples 5 and 6 of the patent, the '920 patent; do you recall that? 10:36:13

A. I do.

Q. I'd like to hand to you, Dr. Benet, what has been previously marked as Inysis Exhibit 1001.

MS. HUFNAL: Object to testimony on this document. Outside of the scope of the declaration.

BY MR. MONCO:

Q. Now, again, you reference the '920 patent in your declaration, correct?

A. I did.

Q. And we saw counsel going through the list of documents you had, and that included the '920 patent, correct?

A. It did.

Q. Now, do you recall any questions -- do you recall the questions that counsel asked you with regard to bell-shaped curve and sigmoidal curve -- not sigmoidal curve but sigmoidal graph? 10:37:04

MS. HUFNAL: Objection to form.

THE WITNESS: I do.

BY MR. MONCO:

Q. To your knowledge, Dr. Benet, is there any evidence in the '920 patent, Exhibit 1001, that would support the conclusion that the data shows a bell-shaped curve?

MS. HUFNAL: Objection to the form. Outside the scope of the testimony and the declaration. 10:37:33

THE WITNESS: No, no data in the patent to suggest that there is a bell-shaped curve for CBD in these analyses.

BY MR. MONCO:

Q. During your review of the '920 patent, what's the nature of the data that is shown in the '920 patent?

MS. HUFNAL: Objection. Outside the scope of the examination and the declaration.

THE WITNESS: The examination of animal data using the -- well, using a bunch of examples but relying on pilocarpine and penicillin seizure data in Examples 5 and 6. 10:38:12

BY MR. MONCO:

Q. What type of animals were used in the '920 patent?

MS. HUFNAL: Same objections. Outside the scope.

THE WITNESS: Rats.

BY MR. MONCO:

Q. And in your list of documents that you identified in your declaration, counsel also referenced the Cunha reference; do you recall that? 10:38:27

A. I do.

Q. What's the -- what type of data is used in the Cunha reference?

A. Human data.

Q. Based on your expertise in determining the

significance or the importance of the data for ultimate clinical use in humans, what reference would you -- would you rely on references pertaining to human data more than you would with regard to animal data?

MS. HUFNAL: Objection to the form. Outside the scope.

THE WITNESS: I would. I would.

BY MR. MONCO:

Q. You would what? 10:39:16

A. Give a preference to human data over animal data.

Q. Referring to the '920 patent -- and I believe you said you testified that they relied on rat data -- was there anything in the '920 patent that would -- or is there anything in the '920 patent that shows how you would convert the dosage for the rats to dosage for humans?

MS. HUFNAL: Objection to form. Outside the scope of the declaration and the examination. 10:40:20

THE WITNESS: In lines -- in column 13 at lines 36 through 39, the authors of the patent show how they convert this CBD data in rats to humans and come up with at least 600 milligrams and optionally between 400 milligrams and

800 milligrams for CBD.

BY MR. MONCO:

Q. In your opinion is that a correct calculation?

MS. HUFNAL: Object to the form. Outside the scope.

THE WITNESS: No, it's not.

BY MR. MONCO:

Q. Why not?

MS. HUFNAL: Outside the scope of the declaration and the examination. 10:41:16

THE WITNESS: Apparently, what the patent writers have done is misinterpret the way that you convert animal data to human data, rat data to human data. What they've done is take the number that is used to convert milligrams per kilograms to milligrams per meters squared. That's the number of six in rats.

But the appropriate way to calculate animal data to human data, according to the FDA guidance, is you take a rat number of 0.16. You multiply it by the dose and multiply it by the weight. 10:41:51

If you take the data of 100 milligrams per kilograms in rats, you would come out with over a thousand as the data that you should have had

suggested the data in Examples 4 and 5 show efficacy.

They showed -- they carried out studies with 1 milligram per kilogram, 10 milligrams per kilogram and 100 milligram per kilogram.

They state that it's significant that 100 milligrams per kilogram and close to significant or almost significant at 1 milligram and 10 milligrams. 1 and 10 milligrams, with the correct calculation, would come out to be a human dose of 10 milligrams or 100 milligrams in a human, which are doses less than Cunha used. 10:42:37

But the 100 milligram per kilogram dose in rats comes out to a value of a thousand. And that's using an average body weight of 65 kilograms, which in the United States is hard to imagine that's an average body weight. So at the low end the calculation that they should have used would have said that the data is a thousand, not 600.

BY MR. MONCO: 10:43:10

Q. Based on that analysis that you just described, what is your opinion regarding the foundation for the dosage in claim 1 of 400 milligrams?

MS. HUFNAL: Object to form. Outside the scope

of the declaration and the proceedings of the IPR.

THE WITNESS: No basis for the 400 milligrams. There is no scientific basis for the 400 milligrams or the statement of preferably between 400 and 800.

MR. MONCO: We have no further questions.

MS. HUFNAL: Five minutes, please.

(A short break was taken.)

MS. HUFNAL: Back on the record.

We have no questions.

(Whereupon the proceedings concluded at 10:52 a.m.)

DECLARATION UNDER PENALTY OF PERJURY

I declare under penalty of perjury that I have read the entire transcript of my deposition taken in the above-captioned matter or the same has been read to me and the same is true and accurate, save and except for changes and/or corrections, if any, as indicated by me on the DEPOSITION ERRATA SHEET hereof, with the understanding that I offer these changes as if still under oath.

Signed on the _____ day of _____, 20__.

_____

LESLIE BENET, PH.D.

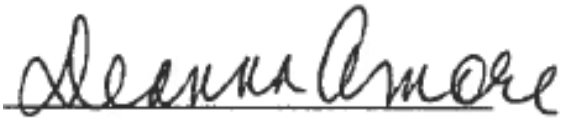
C E R T I F I C A T E

I, DEANNA AMORE, a Shorthand Reporter and notary public, within and for the State of Illinois, County of DuPage, do hereby certify:

That LESLIE BENET, PH.D., the witness whose examination is hereinbefore set forth, was first duly sworn by me and that this transcript of said testimony is a true record of the testimony given by said witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 12th day of October, 2017.



Deanna M. Amore, CSR, RPR

[& - anticonvulsant]