UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE, S.A. and ROCHE PALO ALTO, LLC,

Plaintiffs,

-vs-

DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD.

Defendants.

CIVIL ACTION NUMBER:
11-3962

TRIAL

Clarkson S. Fisher United States Courthouse
402 East State Street
Trenton, New Jersey 08608
June 8, 2015

B E F O R E: THE HONORABLE MARY L. COOPER
UNITED STATES DISTRICT JUDGE

Certified as True and Correct as required by Title 28, U.S.C., Section 753

/S/ Regina A. Berenato-Tell, CCR, CRR, RMR, RPR
/S/ Carol Farrell, CCR, CRR, RMR, CCP, RPR, RSA

United States District Court
Trenton, New Jersey

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WITNESS	VOIR DIRE	DIRECT	CROSS	REDIRECT	RECROSS
David G. Frame					
By Mr. Imbacuan					
By Mr. Ashkenazi					

(In open court. June 8, 2015, 9:30 a.m.)

THE COURT: Good morning, everybody.

ALL: Good morning, your Honor.

THE COURT: Okay. Mr. Lombardi, do you have a witness?

MR. LOMBARDI: Yes. DRL is going to be presenting our next witness.

THE COURT: I see. Mr. Imbacuan, good morning.

MR. IMBACUAN: Good morning, your Honor.

MR. DITTMANN: Your Honor, if I may?

THE COURT: Yes, sir. Mr. Dittmann.

MR. DITTMANN: Briefly, we wanted to address first an issue that has come up, and we discussed it briefly previously, but it's now been crystallized, and we'd like to present it to your Honor, if I may, at this time with respect to the deposition testimonies of Dr. Markman. Can I present that to you briefly now?

THE COURT: Whatever. He is our witness this morning, no?

MR. DITTMANN: He is someone that we intend to call this week, at least through his deposition testimony.

If you recall shortly before trial, Dr. Markman, we were told, was not going to come to trial. We attempted to procure his testimony, his appearance in our case, but he's not available, and that's fine. We, of course, have no issues

with that. And what we had was an agreement with defendants, which this letter, if I can, hand up to your Honor.

THE COURT: Mr. Dittmann, I'm not sure we're going to do this right now. We have a witness here. Is it necessary?

MR. DITTMANN: It is because we're about to begin our case, and we need to know our order of proof, and part of that is Dr. Markman. And we think that Dr. Markman's testimony is particularly appropriate, considering Dr. Frame is about to testify.

It's plaintiffs' position that some of the things you're about to hear from Dr. Frame are directly contrary to what Dr. Markman testified to in his deposition, and we've set forth all these positions in this letter that you've asked for, which we can hand up to your Honor.

THE COURT: Okay. Hand it to me, and I'll look at it during the break.

MR. DITTMANN: Okay.

THE COURT: Then I'll know what you're talking about.

MR. DITTMANN: Thank you.

THE COURT: Sure.

Anything else at the moment?

MR. SENDER: Judge, on the same topic, we had objected, since Dr. Markman was our expert, and we can hand you a letter, as well.

THE COURT: Do you have one?

A. So, CINV, so chemotherapy-induced nausea and vomiting is typically classified in a few different ways.

So, I give you chemotherapy, okay? Within the first 24 hours if you have nausea and vomiting, we call that acute nausea and vomiting. If you have nausea and vomiting past 24 hours, we call that --

THE COURT: You mean onset past 24 hours, or enduring past 24 hours?

THE WITNESS: Either way. So anything that happens past 24 hours, we call delayed nausea and vomiting. And I'll be honest with you, there's no magic to why that is 24 hours. It was literally set as a tool to be able to have different endpoints to be able to do research and evaluate your antiemetics.

There's no necessarily special, absolute time frame that everything changes at 24 hours. It's just used for convention.

BY MR. IMBACUAN:

Q. Is the same delineation used for post-operative nausea and vomiting?

A. So, it is -- it is similar. It's not really been -- I don't think it's been set in stone quite as much as what we have in CINV, and people have a little bit different opinions on when is your higher rate of post-op nausea and vomiting.

A lot of that occurs much earlier than what you see

with CINV, but a lot of the trials do use a 24-hour endpoint for PONV, as well.

Q. Before palonosetron, were there any 5-HT_3 antagonists commercially available?

A. Yes, there were. There were three before palonosetron. One was ondansetron.

THE COURT: You don't have to give its chemical name. That's all right. Ondansetron.

THE WITNESS: Ondansetron.

THE COURT: That will do.

THE WITNESS: Okay.

THE COURT: We're familiar with those names.

THE WITNESS: Okay. Great. Granisetron and dolasetron.

BY MR. IMBACUAN:

Q. Did you review the labels for these 5-HT_3 antagonists?

A. I did.

Q. And do you have a binder up there, Dr. Frame, with some exhibits?

A. I do.

Q. Can we look at DTX-1231? What is DTX-1231?

A. So, this is the package insert from ondansetron, or Zofran®, and it actually comes from what we call the Physician's Desk Reference. And, so, this is essentially a publication that comes out that includes all of the package

inserts for all the drugs.

THE COURT: And this one happens to be dated 2001?

THE WITNESS: Yes, it is.

THE COURT: Okay.

BY MR. IMBACUAN:

Q. Is there another package insert included in DTX-1231?

A. Yes. So, the next one is granisetron. And the third one is dolasetron.

Q. So, based on the package inserts what forms of -- what dosage forms were these prior 5-HT_3 antagonists available in?

A. These were available both orally and intravenously.

Q. Is there a benefit to having an intravenous form of a 5-HT_3 antagonist?

A. So, yeah, there really is for a couple different reasons. One, as you can imagine, if you are having emesis or even if you're terribly nauseated, you really don't want to put anything in your stomach, right? And, so, it is not uncommon that if you're already sick and I give you an oral antiemetic you actually throw it back up, and, so, that's not going to help you. And, so, that's a main -- that's a big reason why you would like to have an I.V. form available.

The other big reason is -- is especially in the oncology setting, so a patient comes in for their chemotherapy, right? We want to make sure that they have good concentrations of that serotonin antagonist so that we can

help prevent that nausea and vomiting.

And, so, you really want to give -- we like to give that as an I.V. drug so that we know it all gets in your system, right? We don't have to worry how much gets absorbed. And we can do it right before we give your chemotherapy so your concentrations are very high as we start to give you your chemotherapy.

And, so, the standard way that almost every oncology clinic gives a serotonin antagonist is as an I.V. form.

Q. Prior to the approval of palonosetron how were the 5-HT_3 antagonists used to treat CINV?

A. So, they were actually used both for acute and delayed nausea and vomiting. As I said, you don't get quite as much benefit out of them usually for delayed nausea and vomiting because, again, serotonin is not your biggest driver later in the game, right?

And, so, when ondansetron -- so just, for example, when ondansetron first came out, okay, we had to compare it to what was our gold standard. And our gold standard at the time was what we call high-dose metoclopramide. So, high-dose -- and the reason we use high-dose metoclopramide is because interestingly at very high doses it would block some 5-HT_3 receptors. But the problem with high-dose metoclopramide is it also causes other problems with the nerves and you become very jittery and you'll just shake and shake and shake. We

call it an extrapyramidal symptom. It also affects your GI tract.

THE COURT: What's that?

THE WITNESS: Extrapyramidal?

THE COURT: Spell "pyramidal."

THE WITNESS: P-Y-A-R --

THE COURT: P-Y-R-A?

THE WITNESS: Yes.

THE COURT: Okay. So, it makes you shaky.

THE WITNESS: Yes. It makes you really, really shake, so, literally I would have patients that literally would be sitting there shaking, but it was better than throwing up 20 times a day.

Sadly, though, once in a while that effect won't go away. So, even though you take the drug away, once in a while patients still wind up with that for a long period of time.

The metoclopramide also plays interactions with your GI tract and actually will often cause you to have a lot of diarrhea. So that's not very helpful either. But that was our -- that was our main standard of care for patients that were -- to prevent emesis in these patients, nausea and vomiting in these patients.

THE COURT: So, that drug isn't regarded as a 5-HT_3 antagonist?

THE WITNESS: It is not because you have to use very,

very high doses, and, so, now I would never, ever do that.

THE COURT: So, it is not considered to be in this class?

THE WITNESS: It is not. No, that's correct.

THE COURT: So, ondansetron was the first 5-HT_3 antagonist?

THE WITNESS: Yes. Exactly. So that was the very first one that was approved, and, so, they did their trials to compare ondansetron to metoclopramide. So even with having all those side effects, the best results we saw was about 40 percent complete response with the metoclopramide. With the ondansetron, that response went up to approximately 70, 75 percent.

THE COURT: For acute?

THE WITNESS: For acute.

They also looked at delayed in those initial trials because that was also one of our standards for delayed nausea and vomiting. And both ondansetron and metoclopramide had about a 60 percent overall response rate for delayed nausea and vomiting. So, it pretty much matched a lot of our standard.

And, so, it became very commonplace, and, actually, even in the Guidelines at the time, to be -- to use 5-HT_3 antagonists for both acute and delayed nausea and vomiting.

BY MR. IMBACUAN:

Q. Dr. Frame, are you aware that plaintiffs' experts have stated that the art had shifted its focus from setrons to NK-1 antagonists at the time palonosetron was being involved?

A. Yes, I do.

Q. And do you agree with that statement?

A. So, I don't totally agree with that statement. NK-1 antagonists -- I'm sorry. Let me back up one second. Sorry.

THE COURT: Can we go back to your schematic, please?

THE WITNESS: Yes.

THE COURT: This is your Slide 6.

THE WITNESS: So, as I described a few minutes ago, we know that there's not only one neurotransmitter, right, not only one of these chemicals that are causing nausea and vomiting.

And, so, at the time it had been discovered that these NK-1 antagonists were also important in nausea and vomiting. And interestingly in the animal models, one of the reasons for the excitement of this is in the animal models it actually had the broadest range as an antiemetic of virtually any drug we had seen, and what I mean by that --

THE COURT: What did?

THE WITNESS: The NK-1 antagonists.

THE COURT: Plural?

THE WITNESS: Yes.

THE COURT: And these are approved drugs?

THE WITNESS: They are now.

THE COURT: Okay. Counsel, I think we need a little more foundation because Dr. Frame knows exactly what he is talking about, but I don't.

NK-1 antagonists, if we're going to talk about them, we need to know a name or names for them, and are they on, you know, the market or are they just in lab work at a given point in time. I don't know.

MR. IMBACUAN: We can move on, your Honor.

THE COURT: Okay.

BY MR. IMBACUAN:

Q. So, Dr. Frame, palonosetron is approved for treating delayed emesis?

A. It is.

Q. And is it the only setron that's approved for treating delayed emesis?

A. It is.

Q. And do you have a view on its approval for treating delayed emesis?

A. So, I do. So, one of the -- one of the advantages of palonosetron -- and we're going to get to this in a little bit I think -- but one of the advantages of palonosetron is it has what we call a very long half-life.

THE COURT: It is eliminated slowly from the body?

THE WITNESS: Exactly. And, so, it has about a

Q. So let's focus --

THE COURT: So that's three?

THE WITNESS: That's three.

BY MR. IMBACUAN:

Q. So there are three press releases in DTX-1022?

A. Yes.

Q. So let's just focus on the October 3rd, 2001 press release, if we could have that on the screen. That's DTX-1022-0004.

You reviewed this press release, right, Dr. Frame?

A. I did.

Q. And what was reported just generally in this press release?

A. So, this press release, the main purpose of this press release was to describe that they had gone on to Phase III trials and that they were completing patient enrollment.

Q. And you said "they." Who are you referring to?

A. I'm sorry. Helsinn.

Q. So let's just go through the press release. Does the press release say anything about Phase I trials that Helsinn conducted?

A. It does. So right here.

Q. Can you read that into the record, please?

A. Yes. So, "Results of Phase I trials in healthy volunteers to assess the pharmacokinetic properties and safety

of palonosetron were presented at the American Society of Clinical Oncology meeting in May of 2001."

It also goes on to say that the elimination half-life that they found was 37 hours.

Q. And how did this compare to the then marketed 5-HT_3 antagonist?

A. So the marketed agents at the time had between approximately four- and nine-hour half-life, and so this was significantly longer.

Q. And was this reflected in the press release?

A. It was. It says that it was at least three times longer than marketed agents.

Q. So, what about Phase II trial, did the press release say -- did this press release say anything about Phase II trials that Helsinn had conducted?

A. It does. So just the next line, it actually says that Phase II trials assessing the efficacy beyond 24 hours were done. And, again, due to the long half-life of the drug, you were able to study it for a longer period of time.

Q. And what does that mean when you say you were able to study it for a longer period of time?

A. Right. So I apologize.

If you look just up a little bit further in the press release, right up here, it says that the efficacy in the Phase II trial was to look at both acute, so the 24-hour duration,

as well as essentially the delayed, or Days 2 through 5.

THE COURT: This is in the Phase III now?

THE WITNESS: No, that was the Phase II.

THE COURT: Well, it says --

THE WITNESS: So --

THE COURT: -- "Based on the extended half-life of palonosetron and the results of a Phase II trial, its efficacy is being assessed over Day 2 through Day 5." How do you read that?

THE WITNESS: Yes. I'm sorry. So they were able -- I apologize.

So they were able to assess -- that's what I was saying -- is they were able to assess this in the Phase II trial, and, yes, it was also being assessed in the Phase III.

BY MR. IMBACUAN:

Q. So you anticipated my next question.

Does this press release say anything about Phase III trials that were being conducted?

A. Yes. And, so, it says that the double-blind randomized Phase III trial compares I.V. palonosetron to currently marketed 5-HT_3 antagonists.

Q. So, based on the press release, Dr. Frame, what can you conclude about how Helsinn was conducting its clinical trials for palonosetron?

A. So, again, this is the very standard way that all

these -- that the majority of these clinical trials are done.

Q. So, Dr. Frame, this is a -- the information about palonosetron is being disclosed in a press release. Does the fact that it's -- the information is contained in a press release make it any less relevant to you?

A. No. So, you know, to me purposes of press releases are to be able to inform you where drugs are at in development. And I'll be quite honest with you. We often have to prepare for drugs coming to market, and so I'm actually even on a Listserv for oncology drugs so that I get press releases so that I can follow where drugs are at so that I can get ready for them to come to clinic.

Q. So it's part of --

THE COURT: We also see sometimes that a drug maker will say, ah, you know, we thought we were going to get this drug to the public, but we had to shut it down in Phase III.

THE WITNESS: That's actually a very good point. You know, press releases don't always just say all the good stuff that they find. You're absolutely right. The press releases will tell you that, what you exactly said, was that, oop, it didn't work. Yeah.

I guess the other thing I will say from this press release is the FDA would not have let you go to a Phase III trial if you did not show an efficacious dose in Phase II.

BY MR. IMBACUAN:

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