UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

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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.

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CIVIL ACTION NUMBER:

11-3962

TRIAL

Clarkson S. Fisher United States Courthouse
402 East State Street
Trenton, New Jersey 08608
June 4, 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

A P P E A R A N C E S:

PAUL HASTINGS
BY: JOSEPH O'MALLEY, ESQUIRE
ISAAC S. ASHKENAZI, ESQUIRE
ANGELA NI, ESQUIRE
SAUL EWING
BY: CHARLES M. LIZZA, ESQUIRE
Attorneys for the Plaintiffs

BUDD LARNER
BY: STUART D. SENDER, ESQUIRE
ANDREW ALLEN, ESQUIRE
Attorneys for the Defendant, Dr. Reddy's Laboratories

WINSTON & STRAWN
BY: JOVIAL WONG, ESQUIRE
GEORGE LOMBARDI, ESQUIRE
JULIA MANO JOHNSON, ESQUIRE
BRENDAN F. BARKER, ESQUIRE
LITE DePALMA, GREENBERG, LLC
BY: MAYRA V. TARANTINO, ESQUIRE
Attorneys for the Defendant, Teva

I N D E X

(In open court. June 4, 2015, 9:30 a.m.)

THE COURT: Good morning, everyone. Okay. Are we ready to go to work today? Would you like to call your next witness?

MR. WONG: Yes. Good morning, Your Honor. My name is Jovial Wong. I represent the Teva defendants. Good to see you again.

As our first witness defendants call Dr. John Freuhauf. He will be discussing more about the efficacy of palonosetron.

(Whereupon, JOHN FRUEHAUF, witness for the defendants, sworn.)

THE DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: John P. Fruehauf, F-R-U-E-H-A-U-F.

VOIR DIRE EXAMINATION BY MR. WONG:

Q. Good morning, Dr. Fruehauf.

A. Good morning.

Q. Dr. Fruehauf, have you been asked to provide expert opinions in this case?

A. Yes, I have.

Q. And, in general, what do your opinions relate to?

A. They relate to the clinical development of palonosetron.

Q. Okay. Let's do a little background first, Dr. Fruehauf. Where are you currently employed?

A. University of California Irvine.

Q. And what is your current position at the University of California Irvine?

A. I'm a professor of clinical medicine and the director of clinical pharmacology and developmental therapeutics.

Q. And is there a particular cancer center that you work at at UC, Irvine?

A. I work at the Chao Family Comprehensive Cancer Center.

Q. And what is a comprehensive cancer center?

A. It is a cancer center -- there are 43 comprehensive cancer centers in the United States, and this is one of those. They're designated by the National Cancer Institute, and they have to have the complete array of services from basic research to clinical trials development to qualify.

Q. How long have you been at UC, Irvine?

A. Since 1993.

Q. Can you briefly describe your educational history?

A. I went to college at UC Santa Barbara where I got a bachelor's degree in psychology and a bachelor's degree in cellular and organismal biology. And then I proceeded to medical school and did an M.D./Ph.D. program at Rush University in Chicago, and my Ph.D. was in pharmacology.

Q. What is pharmacology?

A. Pharmacology is the study of how drugs work.

Q. Okay. After you got your medical degree in 1985 what did

effective at a certain time.

MR. WONG: Okay. Let's go right to the first document. Can we have the Syntex Phase II trials, DTX-0227. Let's go to Page 5 of the study.

BY MR. WONG:

Q. Dr. Fruehauf, do you recognize this document, DTX-0227?

A. Yes, sir. So, this is the final report on the 2330 clinical trial, which is the dose ranging, efficacy, safety, and pharmacokinetic study of single-intravenous doses of RS-25259, which is palonosetron, for prevention of nausea and vomiting in chemotherapy-naive cancer patients receiving highly emetogenic chemotherapy.

Q. Dr. Fruehauf, were you in court on Tuesday to hear Dr. Calderari's testimony on this document?

A. Yes, I was.

MR. O'MALLEY: And I'll just object until they lay the foundation that your Honor requested as to whether or not the POSA would have had this, since the overarching opinion is that a POSA would have known X.

THE COURT: Okay. Mr. Wong, can you -- is this available to a POSA?

BY MR. WONG:

Q. Would this document have been available to a POSA? Was this document publicly available as of 1995?

A. I don't believe so.

Q. If you saw this document in 1995, would you understand that, and reviewing the data, would you understand that palonosetron was effective to reduce CINV?

MR. O'MALLEY: Objection. Calls for speculation.

THE COURT: Sustained.

You can ask him what this document tells him now. That's fine.

MR. WONG: That's fine.

So let's go to Page 14. Let's go right to results or the study synopsis, and let's go to objections down low. The objectives below.

BY MR. WONG:

Q. Dr. Fruehauf, what was a primary -- what was a primary objective of this Phase II study? Looking at this document today, what was the primary objective of the Phase II study?

A. It was, basically, to determine whether palonosetron, over a dose range of 1-90 micrograms per kilogram, given to patients who were treated with highly emetogenic chemotherapy would reduce the likelihood of chemotherapy-related nausea.

Q. Okay. In carrying out the primary objective of this study, would it include a determination of whether palonosetron reduces the likelihood of CINV when administered to humans?

A. Yes.

Right below.

BY MR. WONG:

Q. Dr. Fruehauf, how would you characterize this Phase II Study 2330?

A. This is a very strong Phase II study because it was randomized and double-blinded in multicenter, so in multicenter trials, you have a variety of people participating, which decreases bias.

And then it was this dose-ranging efficacy study, so they wanted to know what dose is working to suppress nausea. So it was a very strong design for a Phase II trial.

THE COURT: You said not all Phase II trials are even blinded at all.

THE WITNESS: Correct.

THE COURT: This was?

THE WITNESS: Yes.

MR. WONG: Okay. Let's go to the next section, the number of subjects section.

BY MR. WONG:

Q. Dr. Fruehauf, how many patients in total were involved in this Phase II Study, 2330?

A. There were 161 patients, more males than females, and then there were 13 patients who were excluded from the efficacy analysis for various reasons, which, you know, we won't go into, but -- and, so, it was 161 patients with 13

excluded.

Q. And how many patients actually got the 0.25 milligram dose of palonosetron?

A. There were -- which is the equivalent of 3-micrograms-per-kilogram dose. Of 3 micrograms per kilogram, .25 was the equivalent to 3 micrograms per kilogram, and there were 24 patients who received that dose.

Q. So, did the study design of this Phase II study allow the determination of whether palonosetron administered at 0.25 milligrams reduces the likelihood of CINV when it was administered to a human?

A. Yes.

MR. WONG: Let's go to summary and conclusion section on Page 15.

BY MR. WONG:

Q. Right here in the first sentence, what was Syntex's conclusion on this Study 2330?

A. They concluded that all four doses, and they're talking about 3, 10, 30 and 90, they didn't -- .3 to 1 was a low dose that wasn't expected to have the full effect, but it did have some effect because no drug would have lead to, you know, zero control of nausea and vomiting.

So, they found that 3, 10, 30 and 90, let's take the percent complete control going across, those were equivalent

effective as compared with the combined results from a cohort of the .3 to 1 micrograms per kilogram.

Q. And what do they state in the first sentence?

A. They state that palonosetron was administered as a single bolus intravenous injection of these doses 30 minutes prior to chemotherapy.

Q. So, let's focus in on the --

THE COURT: And that they were looking at suppressing CINV for 24 hours after the chemotherapy.

THE WITNESS: Yes, ma'am. So, the endpoints here were complete control at 24 hours, which means, by definition in the study, that they didn't throw up and they didn't feel nauseated. They didn't need a medicine to help them after they got the first medicine.

And then this is a second endpoint, complete response, where the numbers were a little lower because that would be those patients might have needed some rescue medicine, and then the median time --

THE COURT: What's the difference between complete control at 24 hours and complete response at 24 hours, can you tell us?

THE WITNESS: Yeah, this is really the difference between who needed a rescue medication, and the percentage of people -- like this is a lower number for complete response because they might have felt nauseated. They didn't throw up,

but they might have felt nauseated. They filled out a questionnaire --

THE COURT: Yes.

THE WITNESS: -- about how they felt over the 24-hour period --

THE COURT: Yes.

THE WITNESS: -- and they used that questionnaire to assess the benefit of the drug for its intended effect.

THE COURT: And that last row says, "median time in hours to failure defined as first emetic episode or rescue drug."

THE WITNESS: Yes. So that is, you know, basically, they got the medicine, they got the chemotherapy, and how long did the medicine work for? When did it wear off?

So when it wore off, that means you're starting to feel sick. And that's the delayed emesis. And, so, let's say for the .25 or the 3-micrograms-per-kilogram, that time to failure was 22.7 hours, compared to, let's say, 19 for 10, greater than 24 for 30, and 21.8 for 90. We can see these numbers are all pretty consistent, but these numbers are lower, so there's sort of a --

THE COURT: In other words, the dosage beginning with 3 and going up was pretty consistent. It's just the dosage below 3 that fell off.

palonosetron is it was very potent. And, you know, you're binding to a receptor, and if you -- if you have enough drug to bind to all the receptors and they're all blocked at a certain dose, giving more drug won't have any more benefit.

THE COURT: Doctor, we're talking about this H --

THE WITNESS: 5-HT.

THE COURT: -- 5-HT_3 receptor. That's not the only receptor that sends signals of nausea to the brain, is it?

THE WITNESS: No. As I was explaining earlier from my practice, I will combine drugs that will work on different receptors because here there's only a 50 percent control.

THE COURT: Even at best --

THE WITNESS: Even at best.

THE COURT: -- with palonosetron.

THE WITNESS: With one drug. So, if you give a second drug and a third drug, now you're going to improve your control rate to some degree; but, of course, as you add more drugs, you're getting into more side effects.

THE COURT: But the other drugs would target other receptors theoretically.

THE WITNESS: Correct.

THE COURT: Thank you.

THE WITNESS: So, here we have a saturation of the receptors, and as you go higher, you don't really see any change after that.

BY MR. WONG:

Q. Let's just focus on the 0.25 milligram data that's under 3-microgram-per-kilogram. What do the data, 46 percent, 39 percent and 22.7 hours, based on those data what can you conclude about whether 0.25 milligrams of palonosetron reduced the likelihood of CINV in patients who got this dose?

A. It's very clear that it effectively reduced the risk. I mean, if there was zero here, from my clinical experience if you don't give any premedication to someone who's getting highly emetogenic chemotherapy, 90 percent of them are going to throw up.

THE COURT: Because that's nature's way --

THE WITNESS: That's nature's way.

THE COURT: -- is that right?

THE WITNESS: They get a poison, they want to throw up. So, you have to have something in there to suppress that natural reaction to the poison that we're putting in their veins.

And, so, this was partially effective, and then this was the maximal effect, I think, in this Phase II trial.

THE COURT: You're referring to the Column 3.

THE WITNESS: Yes.

THE COURT: The column under the Dosage 3.

THE WITNESS: Right. So this is -- these percentages