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

WITH SEALED PORTIONS

Clarkson S. Fisher United States Courthouse
402 East State Street
Trenton, New Jersey 08608
June 15, 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
ERIC W. DITTMANN, ESQUIRE
ISAAC S. ASHKENAZI, ESQUIRE
SAUL EWING
BY: CHARLES M. LIZZA, ESQUIRE
Attorneys for the Plaintiffs

BUDD LARNER
BY: STUART D. SENDER, ESQUIRE
MICHAEL H. IMBACUAN, ESQUIRE
HUA HOWARD WANG, ESQUIRE
CONSTANCE S. HUTTNER, ESQUIRE
KENNETH E. CROWELL, 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 15, 2015, 9:30 a.m.)

THE COURT: Good morning, everyone.

ALL: Good morning, your Honor.

THE COURT: How is everybody today?

ALL: Good.

THE COURT: Okay. What would you like to start with this morning?

MR. ASHKENAZI: Your Honor, we're planning on playing some deposition designations this morning.

THE COURT: All right. Is there any dispute about them, these?

MR. ASHKENAZI: Not that I'm aware of.

MR. SENDER: Other than the sort of the standing 403 objection to our experts who did not appear, you know, we've designated what we could out of it to try to provide some context.

THE COURT: All right. Well, I'll see them, and I'll rule at some point. But we'll definitely know what we're delineating as your objection.

MR. SENDER: Thank you, your Honor.

MR. LIZZA: Your Honor, in that regard as requested by your Honor for the line-by-line analysis, we've prepared a chart with the designations and with our basis for relevance and probative value. So if I may approach, I can hand that chart up.

THE COURT: Sure. Have you served it?

MR. SENDER: No, they have not, your Honor.

MR. LIZZA: We're serving it now.

THE COURT: Okay. And, again, you don't need to respond until you've had a chance to digest it and me, too. Okay? Fine.

MR. ASHKENAZI: Your Honor, at this time, we'd like to play the deposition designation of Dr. Maurie Markman who is DRL's expert clinical oncologist. According to DRL, Dr. Markman is the president of medicine and science at Cancer Treatment Centers of America. Dr. Markman has more than 20 years of experience in cancer treatment. He has held clinical, research, teaching and management positions in several highly regarded medical institutions in the U.S.

Dr. Markman has extensive experience with all the 5-HT_3 receptor antagonist drugs approved in the U.S. Dr. Markman was deposed regarding his expert opinions in this case.

And for the record, your Honor, we have a binder with the corresponding deposition exhibits. Markman Deposition Exhibit 1 corresponds to DTX-1206.

THE COURT: I'm sorry. Just a second, please. I'll tell you when I'm ready.

MR. ASHKENAZI: Okay.

THE COURT: Was he deposed once or twice?

Q. And do you agree with Dr. Kirsch?
A. No, I do not.
Q. Why not?
A. Well, I prepared a few slides to illustrate why the compound in the Won publication would not be relevant to a POSA looking at palonosetron, so -- this kind of gets kind of technical.
THE COURT: For stability purposes?
THE WITNESS: For stability purposes, yes. This gets kind of technical, Your Honor, but ask questions if you have any questions.
THE COURT: Okay.
THE WITNESS: But, yeah, so we've looked at the structures and the chemistry here, and I do not agree with Dr. Kirsch.
BY MR. DITTMANN:
Q. So why don't we take a look at the demonstrative you've mentioned starting with PDX-712.
A. Yes.
Q. Can you explain what you see here, Doctor?
A. So, here I've highlighted in the chemistry -- the chemical, the element difference between the Won compound which is RG 12915, that's the compound that Dr. Kirsch referred to, and here's the palonosetron.
You can see that the chemical difference here, this is

a cyclic lactam versus a linear lactam, and you have a benzofuran here. You do not have that. And you have cyclohexane with a fairly rigid structure here -- I'm sorry.
THE COURT: Can you slow down just a little with the words.
THE WITNESS: I'm sorry. Okay. Where do you want me to back up to?
Okay. So that this is a linear amide, and this is a cyclic lactam, this is a cyclic amide, a more rigid structure indicated by the -- the dash lines here indicate the stereochemistry of this molecule that's not indicated here. Because there isn't stereochemical issues here in this molecule, but these there are.
And you can see the difference in the chemical structures in this two-dimensional representation of the chemical structure. So the chemistries of these two molecules are quite different.
BY MR. DITTMANN:
Q. Now, Dr. Amidon, just to make the record clear, if we could, going back to the Won molecule starting on the left, the top part of the molecule, here, can you explain with the O, H, and N, next to the --
A. So this is --
Q. Can you explain what that is again?

called a linear amide. This is an amide. And this is an amide, too, but it's connected to a cyclic. It's a cyclic amide, so we call this a lactam, most common --
THE COURT: That's on the palonosetron side?
THE WITNESS: In the palonosetron, it's a cyclic lactam. I mean, this is a six-membered lactam. I mean, the lactams are famous, beta-lactam antibiotics, but this is not anything like that.
But this is a cyclic amide, a very unique structure, as opposed to the linear amide here. This is the amide bond and this is the amide bond here.
BY MR. DITTMANN:
Q. It may be helpful if we can bring up PDX-713 and continue our discussion.
A. Yeah, okay.
So, I think Dr. Kirsch was highlighting this similarity, and that is true, obviously. There is a quinuclidine -- well, okay, this is a tri- -- we'll get into this, but this is a triamine, but it's a particular quinuclidine, and that part of the molecule, just that part, highlighted in the light green is the same.
THE COURT: In both?
THE WITNESS: In both molecules.
THE COURT: In both molecules?
THE WITNESS: Molecules, yeah.

But the -- the rest of the molecules are quite different.
And so the chemistry is, of course, highly dependent on the actual chemical structure and chemical bonding. So these are quite different molecules.
BY MR. DITTMANN:
Q. Bring up PDX-714.
THE COURT: The fact that you've got a ring, a ring structure in the palonosetron, connecting up -- please forgive me. I'm not a chemist --
THE WITNESS: I -- I --
THE COURT: -- the O, the N, and the H.
THE WITNESS: Yes.
THE COURT: You say that that's a -- that's a tighter structure than the linear one that the Won has connecting those three atoms?
THE WITNESS: Yes, yes. It's more rigid, it's more structurally fixed spatially, yes, because of the bonding structure of carbon and nitrogen, yes.
BY MR. DITTMANN:
Q. And do you have a slide discussing this rigidity you're mentioning?
A. Yes, I think I've illustrated that on another slide.
Q. Can we bring up PDX-714?

A. Yes. So, here, it's kind of summarizing that point, Your Honor, here. This is a more flexible, you're going to have cis and trans, this quinuclidine versus the hydrogen, this part.

THE COURT: You have what?

THE WITNESS: I'm sorry. Okay.

BY MR. DITTMANN:

Q. Doctor, what might be helpful if you --

A. I'm sorry.

Q. -- point to the left side, and say, we're talking about Won and then we'll move to the right side next. Is that okay?

THE COURT: Yeah. We have two things we're contending with here. We're making a record, so the pointer, when it's on, one --

THE WITNESS: You don't -- yeah.

THE COURT: -- one drawing or another, the words have to say, now I'm comparing what we see here on the left with what we see here the right. And the other, of course, is the comprehension, the communication gap.

THE WITNESS: Okay. Okay. Well, just slow me down.

THE COURT: And also, the other thing is that the court reporter has to be able to get these words down.

THE WITNESS: I understand. I understand. Just slow me down.

THE COURT: Just take your time.

THE WITNESS: This is not an environment I'm used to teaching in so...

So, on the left, with the Won compound, the RG 12915, this structure is free to move, in fact, the hydrogen and this carbon can change position and we call it cis/trans. And so this is more flexible here. While this cyclic structure fixes this nitrogen in a chemical position. Okay? So that was my -- that was the essential point of that.

THE COURT: Okay. And you've used the term "flexible" for the Won at that location, and "rigid" for the palonosetron at that location?

THE WITNESS: Correct. Correct. Correct.

And then I highlighted here also that there's different elements. There's a chlorine and an oxygen in the Won compound, which would make the chemistry of the Won compound quite different.

So, in conclusion, this is maybe getting a little technical, but the Won -- the compound on the left, the Won compound, is a different chemical structure than the palonosetron, and so a POSA would look at it and say, it's not much help to me with regard to predicting palonosetron properties.

THE COURT: Including stability?

THE WITNESS: Including stability.

THE WITNESS: The stability is very dependent on the electronic structure and the elemental structure of the molecule.

BY MR. DITTMANN:

Q. Just to take one step back, Doctor, to make sure that the record is clear, you were talking about the chlorine and oxygen on the Won molecule, if you see on the left side of the demonstrative, and we see here there are labels "activator" next to both. Can you explain what you mean by "activator"?

A. Well, there's -- for chemical reactivity, there would be more reactive, more chemically reactive.

Chlorine has got more electrons around it as an atom and oxygen has got two -- lone pairs, so there's more electron -- lone-pair electrons. Lone-pair electron, that's a function of the bonding structure of chlorine and oxygen. So there's more electron freedom, more electrons free in the oxygen and the chlorine.

So activator is -- that's just illustrating that these compound -- the Won compound on the left with the chlorine and oxygen is electronically a very different structure than the palonosetron compound on the right.

BY MR. DITTMANN:

Q. So, turning to the palonosetron on the right, do you see any such activators present in the structure of that molecule?

A. No.

Q. Now, just to summarize, what -- where we are so far, you know, what would a POSA infer, if anything, with respect to stability looking at the structural differences between these two molecules?

A. I believe that the Won compound on the left would be of no help, so there'd be no useful information from the Won compound that you would extrapolate to the palonosetron compound. So I would say you would learn nothing about palonosetron from the Won compound.

THE COURT: Now, Doctor, this drawing, chemical drawing of the palonosetron molecule, doesn't show up in the '333 patent. That's what we've heard so far in the evidence. Would you agree with that?

THE WITNESS: The chemical -- okay.

THE COURT: Chemical drawing.

THE WITNESS: The chemical drawing of the Won compound on the left is only generically included in the '333 patent.

THE COURT: But I'm talking about the palonosetron on the --

THE WITNESS: I'm sorry, the palonosetron, okay. The palonosetron compound in the '333 patent, I'm sorry. I was confused, Your Honor.

Correct, the palonosetron compound in the '333 patent

and the symbols that they have in there.

If you assemble -- if you look into that in all of the potential compounds, you will find palonosetron is one of the compounds in that -- that's contained in the structures that were in the '333 patent.

THE COURT: That I get.

THE WITNESS: Yeah.

THE COURT: I just wanted to establish, you've looked at the '333 patent, and this chemical drawing of the palonosetron molecule is not drawn in the '333 patent. But what we've learned so far in the evidence here, I just want to check with you on this, the actual palonosetron molecule is verbally described in the '333 patent, it is called out and described.

THE WITNESS: That's my understanding, it was called out and described but not structurally presented, yes.

THE COURT: Okay.

THE WITNESS: Yeah.

BY MR. DITTMAN:

Q. Do you understand that Dr. Kirsch relies on a Clark 1993 reference, DTX-282, in asserting that those -- the prior art recognized similarities between the Won molecule and palonosetron?

A. Yes, I'm familiar -- I'm aware of that testimony, yes.

Q. And do you understand Dr. Kirsch has contended that a

POSA would have focused on the Clark 1993 for whatever information they can glean about compounds that are related to palonosetron that may inform them about their efforts to develop a stable palonosetron formulation?

A. Well, I think a POSA might -- might have been aware of the Clark reference, but the Clark reference was focused on developing a pharmacophore model and used crystal structure, so I think it would be of little assistance. But I think I have some transparencies on that, but I did look at the Clark article and I think it does not say anything regarding chemical stability.

Q. Can we bring up the Clark reference, DTX-282? And, first, if we can focus on the abstract. Thank you.

Can you -- I think you started to summarize this, Doctor, but can you explain to the Court what Clark 1993 was focusing on?

A. Well, okay. There's a lot of technical chemical details in here.

I would just point to the last line in the abstract. Computer modelling here, computer modelling studies were performed, and previously forward -- previously reported 5-HT_3 receptor antagonists -- previously reported -- I'll speak more slowly -- 5-HT_3 receptor antagonist pharmacophore models were refined to include a lipophilic binding domain.

pharmacophore model -- models which was research -- a research effort in the 1990s to try and reverse engineer a receptor, and they're looking for 5-HT receptor antagonists, things that bind to this receptor. And they wanted to reverse engineer what the receptor looked like.

It's -- it was not a very successful line of research, but that's what this paper -- my point is, this paper focused on a pharmacophore model and based on the crystal structure of the molecules. So it had little -- little applicability to solution conformation which would be more freedom in the solution than in the solid state. So this -- this paper is of, I would say, no help to a formulation scientist.

Q. Just to be clear, was Clark 1993, in your view, addressing any stability-related issues?

A. No.

Q. Can we turn to Page 5, please. I want to focus on the right column, yeah, you have it there, correct.

A sentence I'll read into the record that states: "In fact, a crystal structure of another 5-HT_3 antagonist (44) has the conformation of the quinuclidine ring system in a similar conformation to the overlap conformation of (S,S)-37." Do you see that, Doctor?

A. Yes.

Q. And, first, do you understand this to be a sentence that Dr. Kirsch focused on in his testimony?

A. Yes. This is my understanding that the sentence that -- that Dr. Kirsch referred to, and the sentence particularly focuses on the quinuclidine part, just that upper right-hand part of the molecule. And those two, the -- that's a tricyclic with a nitro- -- bridge nitrogen, that's a very fixed structure, so this is not really saying anything other than that's fixed. That's the same in the two molecules.

Q. Just for context, if we can bring up the structures below that sentence, just to make sure we're all following along.

A. Yeah. This is the quinuclidine part.

Q. So you're pointing to the upper right portion of the molecule?

A. Yes.

Q. Compound 44?

A. Yes.

Q. Okay. If you go back to --

THE COURT: With the jagged line through it?

THE WITNESS: Yes, that means it's a tricyclic. This is the cycle, this is a cycle and this is -- this is a very rigid structure that you can do. Six-membered rings are common in organic chemistry.

BY MR. DITTMANN:

Q. Now, in the sentence we were looking at from Clark 1993, 44 is a reference to this Compound 44 shown below, the text

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