UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ASTRAZENECA PHARMACEUTICALS LP, et al., Plaintiffs/Counterclaim-Defendants, -vs- SAGENT PHARMACEUTICALS, INC., Defendant/Counterclaim-Plaintiff.	CIVIL ACTION NUMBERS: 14-cv-03547-RMB-KMW
ASTRAZENECA PHARMACEUTICALS LP, et al., Plaintiffs/Counterclaim-Defendants, -vs- GLENMARK GENERICS, INC., USA, Defendant/Counterclaim-Plaintiff.	14-cv-05539-RMB-KMW
	15-cv-00615-RMB-KMW

Mitchell H. Cohen United States Courthouse
One John F. Gerry Plaza
Camden, New Jersey 08101
July 14, 2016

B E F O R E: THE HONORABLE RENÉE MARIE BUMB
UNITED STATES DISTRICT JUDGE
AND A JURY

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Certified as true and correct as required by Title 28, U.S.C., Section 753.

/S/ Theodore M. Formaroli, CSR, CRR

United States District Court
Camden, New Jersey

THE DEPUTY CLERK: All rise.
(OPEN COURT, July 14, 2016, 9:08 a.m.)
THE COURT: Good morning.
RESPONSE: Good morning, Your Honor.
09:08AM THE COURT: Have a seat.
Okay. Are we ready to continue with the deposition testimony?
MS. PIROZZOLO-MELLOWES: Yes, we are, Your Honor.
THE COURT: Ms. McCleskey, come forward.
09:09AM MR. FREITAS: Yes, Your Honor.
(Laughter.)
THE COURT: Good morning.
MR. FREITAS: Good morning.
THE COURT: Okay. Whenever you're ready.
09:09AM MS. PIROZZOLO-MELLOWES: We left off at Page 140 of the transcript.
THE COURT: Yes, thank you.
MS. PIROZZOLO-MELLOWES: And Ms. Waldron continues the questioning on behalf of defendants.
09:09AM (Deposition read as follows:)
Q. Let's get back to the documents you kept when you were at the Lombardi Cancer Center.
Did I understand you to say that you did keep laboratory notebooks?
09:09AM A. Yes.

Q. Did you have any raw data of any kind?
A. It was in the laboratory notebooks.
Q. It would be pasted in the lab notebooks?
A. Why do you think raw data would not be on the same piece of paper as the lab notebook?
Q. Actually, I don't know one way or the other. I want to know what your particular procedure was.
A. Well, most of the time, you're writing the laboratory notebook. If you get, like, a printout or something, then you would paste that in the laboratory notebook.
Q. Got it. Did you keep anything on the computer?
A. Yes.
Q. What did you keep on the computer?
A. Well, remembering that computers were not as good as they are now, when I got data, I would have to enter it into the computer, like, into a graphing program, for instance, and then it would draw the graph and I would print the graph. But the -- but the data in the computer was the same as in my -- hopefully, as in my lab notebook.
Q. You didn't create, say, Word files and keep them on a computer?
A. Oh, yes, but that's not data.
Q. Okay. I see. What type of information or documents, if any, would you have saved on a computer?
A. The drafts of the paper, the -- after I entered the data

to make a graph, that would be saved, of course, but it would be the data from the lab notebook that I entered. So it's, like, a copy and -- and also the graphics file, picture a graph. I don't know how you would say that, but the graph itself, I guess you would say, that was saved to the computer. But I also, of course, printed it.

Q. Do you have knowledge as to whether anyone in your group had documents saved to a computer that had originated from AstraZeneca?

09:11AM A. I don't have knowledge about anybody else in my group except me.

Q. Did you have any documents originating from AstraZeneca that related to Ms. McCleskey 1998 saved to a computer?

A. Are you speaking about data?

09:11AM Q. Anything. For example --

A. Saved to a computer?

Q. Yeah, like a statement of proposed investigation --

A. Oh, no --

Q. -- sample requests?

09:11AM A. -- no, no.

Q. Did you have data that originated from AstraZeneca saved to a computer?

A. No.

Q. Did you have any binders or personal notebooks separate

09:11AM from your lab notebooks in which you kept information

regarding McLeskey 1998?
A. I had binders with the tumor data, the tumor measurements in pictures of mice.
Q. Any other places where you would have had information related to McLeskey 1998, that we haven't talked about?
A. No.
Q. Now, you mentioned, if I understood you correctly, I believe you testified that you destroyed your technical documents related to McLeskey 1998 in the beginning of June 2014; is that right?
A. Correct.
Q. What did you mean by "destroyed?" How did you destroy them?
A. I just threw them in the trash.
Q. Just a regular trash bin?
A. Yeah.
Q. Where was this trash bin?
A. At my school.
Q. What school?
A. The University of Maryland School of Nursing.
Q. Do you know what happened to the documents after you threw them in the trash bin?
A. No.
Q. When you left Lombardi Center and took your technical documents with you, was it your understanding that that was

okay by the rules, by Lombardi's policies?
A. I didn't have any understanding about that.
Q. Did you know what document retention policies Lombardi would have had in place at the time?
09:12AM A. No.
Q. When you -- I'll just say "you" to start, and then we will be talking about Lombardi Center. When you got a document on a project, say, a certificate of service or MSDS or something like that, what did you do with it? Where was
09:13AM something like that kept?
A. I don't know what a certificate of service is.
The -- we were required to keep MSDSs in the notebook in the lab for all chemicals that we had in the lab, so that's what we did.
09:13AM So MSDSs would be kept in the laboratory notebooks, correct?
(Reading stopped.)
MR. FREITAS: I apologize.
THE COURT: Ask it again.
09:13AM MS. PIROZZOLO-MELLOWES: You have to read -- he inadvertently reread the question.
THE COURT: Yes.
(Deposition read as follows:)
Q. So MSDSs would be kept in the laboratory notebooks,
09:13AM correct?

A. No, not in -- not where we had the data. We had separate notebook for MSDSs.
Q. MSDSs had their own notebook?
A. That's correct.
09:13AM Q. What about certificates of analysis?
A. Didn't usually keep those.
Q. They're -- why not?
A. Didn't feel that we needed them.
Q. Who retained custody of documents as they came in on the
09:14AM McLeskey 1998 project?
A. I don't know what you're talking about, what documents.
Q. Do you recall how samples got shipped into the facility, whether, say, they went to a mailroom or a specific sample depository?
09:14AM A. They went to the mailroom.
Q. And then that -- that would happen?
A. The mail people would bring them to us.
Q. Would you then keep the samples in your lab?
A. Yes.
09:14AM Q. And did I understand you correctly that at the time you were a postdoc in Dr. Kern's lab, you were not aware of the policies and procedures that Lombardi Center had in place with regard to retention of documents; is that right?
A. Not only was I not aware of anything they had in place, I
09:14AM was not aware if -- whether they had anything in place.

Q. If you received ancillary paperwork with samples, such as a certificate of analysis or something like that, what would you have recorded the receipt of that document --

(Reading stopped.)

09:15AM THE COURT: "Would you."

(Deposition read as follows:)

Q. Would you have recorded the receipt of that document in your laboratory notebook?

A. No.

09:15AM Q. Did Lombardi require you to make copies of anything and send them on to a document repository or anything like that?

A. No.

Q. To your knowledge, were the documents that you were keeping in your lab the only copies?

09:15AM A. As far as I knew.

Q. Are you aware of whether copies were ever made of your laboratory notebooks?

A. I think not.

Q. Who had access to your laboratory notebooks besides you?

09:15AM A. Dr. Kern.

Q. Anyone else?

A. Well, the other people in the lab would have, had they wanted it, but I don't know that they ever did --

(Reading stopped.)

09:15AM THE COURT: So could have.

MR. FREITAS: Pardon me.
(Deposition read as follows:)
A. Well, the other people in the lab could have had they wanted it, but I don't know what they ever did -- that they
09:15AM ever did.
Q. In the conversation that you just referred to, when you communicated with Mr. Trock, what did you discuss with Mr. Trock?
A. He -- I think he, I don't remember a whole lot about the
09:16AM conversation, but he said that he had been just about to discard the data from -- from this paper when they called.
Q. When who called?
A. The -- the lawyers that were doing the Teva thing, Mary Burke and company.
09:16AM Q. I'm sorry. I believe you just said, "Mary Burke did not ask me not to destroy documents."
A. She did not say, Don't destroy documents. When she said that, I do not know.
Q. Mary Burke never told you to preserve your documents
09:16AM related to McLeskey 1998?
A. Correct.
Q. Did anyone Mary Burke worked with ever tell you not to -- tell you that you must preserve your documents related to McLeskey 1998?
09:16AM A. No.

Q. Now, I believe you said earlier that you recall speaking with three people at AstraZeneca, Dr. Wakeling, Dr. Vose, and a third person whose name you don't remember; is that correct?
A. Correct.
09:16AM Q. Do you recall approximately how many times you spoke with Dr. Wakeling?
A. Twice.
Q. Was this via telephone or by some other means of communication?
09:17AM A. Telephone.
Q. Who called who?
A. I called him.
Q. Both times?
A. Yes.
09:17AM Q. Why did you call Dr. Wakeling?
A. The first time I called to get him to send me the drug and find out how to administer it to mice. The second time I called to tell him we had used the drug he sent the first time and that I needed more drug.
09:17AM Q. Did Dr. Wakeling require you to fill out any paperwork or do anything in writing before you received samples of drugs?
A. Not me.
Q. Did he require that someone fill out some sort of paperwork before samples would be shipped?
09:17AM A. I don't know.

Q. What did Dr. Wakeling tell you in response to your request that you wanted AstraZeneca to send you samples of drugs?
A. He told me that I should give it to the mice as it outlined in this paper and that he would ship it.
Q. Basically, an okay-I'll-take-care-of-it type thing?
A. Um-hum.
Q. How many times did you speak with Dr. Vose?
A. Once -- that -- assume that he was not the second -- the person I don't know who it is, but --
Q. Right.
A. -- I know I spoke with him once.
Q. Did you ever communicate with Dr. Wakeling in writing either by e-mail or letter?
A. Not that I recall.
Q. Okay. So you said you spoke with Dr. Vose once; is that right?
A. Um-hum.
Q. Was this on the phone?
A. Yes.
Q. Did you ever have any written communications with him?
A. Not to my -- not that I remember.
Q. On the one incident -- one instance that you did speak with Dr. Vose, who called who?
A. I called him.

Q. Why did you call Dr. Vose?
A. Because Dr. Wakeling told me to call him to get preformulated drug.
Q. Do I understand that you talked to Dr. Wakeling about receiving powdered ICI 182,780 and Dr. Vose about obtaining preformulated ICI 182,780?
09:18AM
A. At separate times.
Q. I'm just trying to understand. I think I understand the -- that you talked to these guys about two different things.
Do I understand correctly that you talked to Dr. Wakeling about receiving powdered ICI 182,780?
09:19AM
A. Correct.
Q. And then do I understand correctly that you talked to Dr. Vose about receiving the preformulated ICI 182,780?
A. Much later.
09:19AM
Q. Much later? That's a good point.
Do you recall approximately when, or do you recall the approximate dates on which you talked to Dr. Wakeling?
A. No.
Q. Year?
09:19AM
A. I don't know.
Q. But you know you talked to Dr. Vose much later. What do you mean by "much later?"
A. When I talked to Dr. Wakeling initially, then he sent me the drug, then we used the drug in mice and also in *in vitro*
09:19AM

studies and we used it all up. So I don't know how long that took, but I would say a matter of months, anyway, maybe a year. Then we needed more drug so I called Dr. Wakeling again, that's when he told me to call Dr. Vose.

09:20AM Q. And the powdered ICI 182,780 would have been what you -- what was dissolved in ethanol and then spiked into the peanut oil?

A. Correct.

Q. When you spoke to Dr. Vose, what did he tell you about

09:20AM shipping you samples of preformulated 182,780?

A. He said he would.

Q. Did he say anything else?

A. Not to my remembrance.

Q. Did he require that you do anything before he sent the --

09:20AM sent the files of preformulated ICI 182,780?

A. No.

Q. Do you know whether anyone in your lab had to complete any type of paperwork before AstraZeneca would send the lab preformulated 182,780?

09:20AM A. I do not know.

Q. Who would know?

A. Possibly Dr. Kern.

Q. Okay. And now the third person that you spoke to, was this before or after you talked to Dr. Vose?

09:21AM A. After.

Q. Who called who?
A. I called him.
Q. Did you have any communications in writing with this third person?
09:21AM A. No.
Q. And what was the purpose of calling this third person?
A. I wanted to find out what the -- what was in the drug because I was getting ready to publish a paper. I was getting ready to write the paper, actually.
09:21AM Q. And what did he tell you?
A. He told me --
Q. Do you recall the words he used?
A. No.
Q. But he told you all of the excipients and their
09:21AM percentages?
A. He told me what's in the paper: 10 percent ethanol, 10 percent benzyl benzoate and 10 percent benzyl alcohol brought to volume with the castor oil.
(Reading stopped.)
09:21AM MS. PIROZZOLO-MELLOWES: Your Honor, I think there was a mistake in reading that.
THE COURT: It's -- no, the court reporter took it down correctly, that's fine.
(Deposition read as follows:)
09:21AM Q. You don't recall whether or not he specified the units of

measure?
A. I do not recall.
Q. How did you know to contact this third person?
A. I called the number that was -- that I had been given for
09:22AM Dr. Vose.
Q. And somebody else answered?
A. I don't know if it was somebody else or if it was
Dr. Vose.
Q. So there -- you're saying -- if I'm understanding you
09:22AM correctly, you believe it's possible that it was Dr. Vose that
told you the makeup of the formulation but you're not sure?
A. Well, it was whoever answered the phone. That's all I
can say about it.
Q. I see. But you called Dr. Vose's direct line?
09:22AM A. Yeah. I called the same number I had called previously
to speak with Dr. Vose.
Q. Who gave you Dr. Vose's phone number?
A. Dr. Wakeling.
Q. Who gave you Dr. Wakeling's phone number?
09:22AM A. I don't remember.
Q. Do you recall generally how you knew to call Dr. Wakeling
that he was the person to call?
A. Either Dr. Lippman or Dr. Kern told me, but I don't know
who or when or anything.
09:23AM Q. But do I understand you correctly that you -- with regard

to this third person, that it was a man?
A. Yes.
Q. When you called Dr. Vose the first time, or when you called Dr. Vose, how did you know it was him that answered the phone?
A. I don't remember.
Q. But you feel confident that you were speaking to Dr. Vose the first time?
A. Well, I certainly believed that I was.
Q. At the time, did you believe that the third person that you were talking to was Dr. Vose?
A. I don't recall what I believed.
Q. What do you believe today?
A. I don't believe.
Q. You have no idea who you talked to?
A. Right.
Q. Did you send AstraZeneca drafts of the study protocol that you were going to follow for the research described in McLeskey 1998?
A. No.
Q. Did you ever provide your lab notebooks or raw data to AstraZeneca?
A. No.
Q. Did you record when you received samples from AstraZeneca in your laboratory notebooks?

A. I don't recall.
Q. What was your general practice with regard to recording receipt of samples at the time you were postdoc in Dr. Kern's lab?
09:24AM A. I would unpack them and if they needed refrigeration, I would put them in the refrigerator or the freezer as appropriate.
Q. Did you have a separate practice as to what you would record about the samples received?
09:24AM A. No.
Q. Was it your understanding from the beginning of your postdoc in Dr. Kern's lab that AstraZeneca was the source of 182,780 or was that something you learned later in time?
A. At the beginning, I had no idea there was such a thing as
09:24AM 182,780.
Q. How did you come to find out that? How did you come to find out that AstraZeneca would supply 182,780 to the lab?
A. I'm not sure.
Q. What do you -- what is your best recollection?
09:24AM A. We had meetings of all the researchers, the breast cancer researchers and it may have come up at that, one of those meetings.
Q. From the Lombardi side of things, not the AstraZeneca side of things, but from the Lombardi side of things, was
09:25AM procuring samples as simple as calling and asking for them, or

was there an internal protocol that had to be followed first?
A. I was not aware of an internal protocol.
Q. Do you know how long it took in between the time you talked to Dr. Wakeling and the time that you received the powdered ICI 182,780?
A. I think it was a matter of weeks.
Q. Do you recall how long it took from the time you talked to Dr. Vose to then receive the preformulated ICI 182,780?
A. Probably about the same.
Q. And you personally do not recall filling out any forms or signing anything in regard to samples, correct?
A. Correct.
Q. I want to make sure we're absolutely on the same page.
So before you started, at any time, did you send AstraZeneca a statement of proposed investigation forms?
A. No.
Q. Do you know whether or not Dr. Kern had sent AstraZeneca a statement of proposed investigation forms?
A. No.
Q. No, you do not know, or no, he did not?
A. No, I don't know.
Q. Did you fill out any other forms for AstraZeneca before you started your work on McLeskey 1998?
A. No.
Q. Do you know whether anyone else in your group filled out

any other forms for AstraZeneca?
A. I don't know.
Q. Before starting the work on --
A. I don't know. I know nothing.
09:26AM Q. Did you personally ever request any samples from AstraZeneca in writing?
A. No.
Q. Okay. So you received powdered ICI 182,780 from Dr. Alan Wakeling, correct?
09:26AM A. Correct.
Q. Did Dr. Wakeling send the powdered samples directly to you?
A. I don't recall. I got them, but I don't remember who they were addressed to.
09:26AM Q. You don't have a specific recollection of whether they came directly to you or whether Dr. Kern gave them to you?
A. I opened the package, or I got the package. I don't know if I got the package from a mailman or from Dr. Kern. I don't know.
09:27AM Q. Okay. But you opened the package?
A. Yeah.
Q. Do you recall approximately when that was when you opened the package?
A. No.
09:27AM Q. Was it in 1997?

A. Oh, no. It was way before that.
Q. Way before that? So 1996, 1995?
A. It was before 1993.
Q. Before 1993?
09:27AM A. Yes.
Q. How was the powder sample packaged? Was it in a -- a bottle or -- how did it arrive, do you recall?
A. I think it was just in a little jar.
Q. Would the receipt of that sample have been logged in the
09:27AM lab?
A. No.
Q. Now, if I understand you correctly, Dr. Wakeling gave you information on administration of the drug, correct?
A. Correct.
09:27AM Q. Did Dr. Wakeling send you instructions on how to formulate the 50-milligram per milliliter concentration of ICI 182,780 and ethanol and peanut oil?
A. He didn't send them to me, no.
Q. Did he send you instructions regarding making the
09:28AM formulation?
A. No.
Q. How did you know to do that?
A. He told me over the phone.
Q. Okay. So Dr. Wakeling told you how to administer it, and
09:28AM he also told you how to make the formulation that's recorded

in McLeskey 1998 concerning ethanol and peanut oil?
A. Exactly.
Q. And you testified earlier, I think, that you were actually the person that had actually dissolved the
09:28AM ICI 182,780 in ethanol and then spiked it into the peanut oil?
A. Correct.
Q. Why did you use a concentration of 50-milligrams per milliliter?
A. Because that's what Dr. Wakeling said to do.
09:28AM Q. Dr. Wakeling did not discuss any sort of confidentiality with you --
A. No.
Q. -- when -- when you spoke with him?
A. No --
09:28AM Q. Sorry, it needs to be verbal.
A. Sorry, no.
Q. If you'll turn to Page 698 of Exhibit 5, do you see a paragraph headed, the title Drugs, and then about seven lines down, we see the lined sentence for the experiments depicted
09:29AM in Figure 1, B and C, 50-milligram per milliliter preformulated drug in a vehicle of 10 percent ethanol, 15 percent benzyl benzoate, 10 percent benzyl alcohol brought to volume by castor oil was supplied by B.M. Vose, Zeneca Pharmaceuticals.
09:29AM Do you see that?

A. Yes.
Q. Is this the preformulated drug that we were just discussing that you procured via telephone conference with Dr. Vose?
09:29AM A. Yes.
Q. Approximately when did you receive the preformulated ICI 182,780 from Dr. Vose?
A. All I can tell you is it was before 1993.
Q. The preformed -- both -- you received both the powdered
09:29AM ICI and the preformulated ICI before 1993. Is that what you're saying?
A. Yes.
Q. How do you know that it was before 1993?
A. In 1993, I received a faculty appointment, and then I was
09:30AM no longer a postdoc. And at that point, the animal experiments were done.
Q. Were you the person that opened the package of the preformulated ICI 182,780?
A. Yes.
09:30AM Q. Do you recall how many preformulated samples were sent to you?
A. No.
Q. Do you recall if those samples were in vials?
A. No.
09:30AM Q. How were -- how were the preformulated samples packaged?

A. I don't recall.
Q. What documentation accompanied the preformulated ICI 182,780?
A. I don't recall.
09:30AM Q. Do you recall whether or not there was documentation included with the preformulated ICI 182,780?
A. I don't recall.
Q. If you wanted to try to remember, who would you talk to?
A. Nobody. I mean, I -- there's nobody. I think it's lost
09:31AM to posterity.
Q. So do I understand correctly that at the time you received the preformulated ICI 182,780, you did not know what excipients were present in the formulation -- in that formulation?
09:31AM A. Correct.
Q. Did you have an understanding that the preformulated ICI 182,780 could not be used in humans?
A. Nothing we had in our lab could be used in humans.
Q. Were you given specific instructions from AstraZeneca
09:31AM that it should not be used in humans?
A. I don't recall.
Q. Turning back to Page 698 in the drug section again, you see the text that says, In a vehicle of 10 percent ethanol, 15 percent benzyl benzoate, 10 percent benzyl alcohol brought to
09:31AM volume with castor oil.

Do you recall who actually wrote that text?
A. I did.
Q. Did you test or analyze the formulation in any way?
A. No.
09:31AM Q. Were you told that the preformulated ICI 182,780 that you received should not be administered intramuscularly?
A. I was told to administer it subcutaneously to my --
Q. When the person who answered Dr. Vose's phone gave you the excipients present in the preformulated ICI 182,780, were
09:32AM you sworn to secrecy?
A. No.
Q. Why did you want to include those details in McLeskey 1998?
A. That's how I was instructed to write a paper when I was
09:32AM in my predoctoral, was to include such things.
Q. Have you searched your personal files for all documents relating to either the powdered ICI 182,780 received or the preformulated ICI 182,780 that you received?
A. I don't have any personal files about this.
09:32AM Q. Did I understand you correctly that you do not recall whether or not the person that answered Dr. Vose's phone told you that the percentages were in weight to volume or volume-to-volume?
A. I do not recall.
09:33AM Q. Did you assume that the percentages were either in weight

to volume or volume-to-volume?
A. I don't think I ever thought about it one way or the other.
Q. Have you thought about it since McLeskey 1998 was published?
A. Yes, but I have no basis for knowing which way it was.
Q. So as you sit here today, you don't know whether or not the percentages were in weight to volume or volume-to-volume?
A. I do not know.
Q. So what did you mean when you said "These studies indicate that estrogen independence may be achieved"?
A. I meant that in our engineered model, we achieved estrogen-independent tumor growth in mice through engineering the cell to express in FGF.
Q. So in the context of your experiment, you wanted to use the aromatase inhibitors and ICI 182,780 to shut down any remaining estrogen that might have been present?
A. Yes.
Q. And you wanted to shut down any remaining estrogen so that you could isolate or investigate the estrogen independent cell growth; is that right?
A. Well, we wanted to demonstrate that cells as -- when injected into mice to form tumors, were not affected by -- by different ways of shutting down the estrogen pathway.
Q. So you used the aromatase inhibitors to shut down the

estrogen pathway so you could demonstrate that the hormonal independent cancer cells were not affected and continued to grow; is that right?

A. Continued to make tumors --

09:34AM Q. Continued to make tumors.

A. -- and grow as tumors.

Q. And the same thing -- so you used the ICI 182,780 to act as a pure antiestrogen, shut down any estrogen receptors so that you could see if the estrogen-independent cells would

09:35AM continue to grow?

A. Correct. As tumors --

Q. As tumors?

A. -- in -- in mice.

The reason I keep saying that is, of course, we can

09:35AM grow cells in tissue culture, but I wasn't talking about that. I'm talking about mice.

Q. Okay. So in order to study the hormonal-independent cells, you wanted to deliberately target any remaining estrogen production or any remaining estrogen receptors first;

09:35AM is that right?

A. Correct.

Q. And the reason that you used the aromatase inhibitors in the ICI 182,780 to shut down the remaining estrogen is because they target the body's estrogen differently than tamoxifen

09:35AM does; is that right?

A. Correct.
Q. Okay. At the time you were using the ICI 182,780, because you understood that it would interrupt estrogen-based pathways?
09:35AM A. It would inactivate the estrogen receptor.
Q. Are you saying -- you keep directing me to the fact that this was -- these experiments were done in mice.
Are you saying that this work has no applicability to human subjects?
09:36AM A. I don't know of any applicability to humans.
Q. The title says Cross-Resistant *in Vivo*.
What does "cross-resistant *in vivo*" mean?
A. "Cross-resistant" means that the cells formed big tumors even in the face of the ICI 182,780, or the aromatase
09:36AM inhibitors. And "*in vivo*," refers to the fact that we used mice or an animal to test it. *In vitro* would be, like, cell culture.
Q. So what does "cross-resistant" mean here? Resistance to several different types of drugs?
09:36AM A. It means also resistant.
Q. So it's basically saying resistant to several types of drugs?
A. Yes.
Q. So this -- okay.
09:37AM Now McLeskey 1998 was published in the Journal of

Clinical Cancer Research, correct?
A. Correct.
Q. And you were the person that determined whether or not you wanted to cite references in McLeskey 1998?
09:37AM A. Me and Dr. Kern.
Q. Did you keep laboratory notebooks from your lab when -- when you -- you were at Georgetown?
A. Of course.
Q. What happened to those lab notebooks?
09:37AM A. I brought them to Maryland with me and then when I was getting ready to retire, I threw them away.
Q. With the rest of the documents?
A. Mm-hmm.
Q. Going back to the preformulated samples that you received
09:37AM from Dr. Vose, if I understand you -- understood you correctly, you thought that you had received the samples before 1993.
A. Yes.
Q. Is it possible that you received them in the first
09:37AM quarter of 1993?
A. I don't think so, but I don't know really.
Q. You don't know for sure one way or the other?
A. Well, we had finished the animal experiments by the time I got my faculty appointment.
09:38AM Q. When exactly did you get your faculty appointment?

A. I believe it was July 1st, 1993.
Q. Okay. So you knew -- you think you received the samples before July 1, 1993?
A. Well, you know, the experiments with the tumors were several months ago, several months long. So it had to have been quite a bit before July.
Q. Okay. So you do or do not think it's possible that you received the samples in early 1993?
A. I don't know.
Q. Okay. When you were talking to the unnamed person that answered Dr. Vose's phone, did you ask who you were talking to?
A. I don't recall.
Q. But you do recall that you talked to Dr. Wakeling twice?
A. Yes.
Q. And you do recall that you were the one that called him both times?
A. Yes.
Q. And you do recall that he gave you instructions on how to make the peanut oil formulation?
A. Yes.
Q. And you do recall that he gave you instructions on administration of the formulation?
A. Correct.
Q. And he's the person that told you to talk to Dr. Vose

about the preformulation -- preformulated ICI 182,780?
A. Yes.
Q. And you remember calling Dr. Vose regarding the preformulated drug, correct?
09:39AM A. Yes.
Q. Okay. But you don't remember whether there was a label on the preformulated drug vials that you received, correct?
A. I'm sure there was, but I don't remember one.
Q. You don't recall whether there was any paperwork that you
09:39AM received with the samples?
A. I don't recall.
Q. You can't remember the name of the person that told you the identity of the formulation?
A. No.
09:39AM Q. But do you remember that the person did not tell you to keep the formulation secret, correct?
A. Yes, I remember that.
Q. You don't remember anything else in particular that he said?
09:39AM A. No.
Q. After you finished the experiments that are reflected in McLeskey 1998, was there any preformulated drug left over?
A. I don't remember.
Q. If there had been drug left over, what would you have
09:40AM done with it?

A. Discard it.
Q. How?
A. Down the sink probably.
Q. You don't recall any specific instructions from AstraZeneca to return any unused material?
A. No.
Q. When you talked to Dr. Wakeling about the ethanol peanut oil formulation, did he say anything other than tell you the order of the steps?
A. Not that I recall.
Q. Did he tell you anything about the development of the formulation within AstraZeneca?
A. No.
Q. I recall asking you about AstraZeneca, and I recall asking you about O'Melveny & Myers. I just want to make sure we're clear.

Did anyone at any time ever tell you to preserve your documents that related to McLeskey 1998?

A. No.
Q. Did I understand you correctly that you were not privy to any sort of confidentiality agreement between AstraZeneca at Lombardi, correct?
A. Correct.
Q. Dr. Wakeling is the person that informed you of the existence of the preformulated drug?

A. Correct.
Q. Dr. McLeskey, may I direct your attention to Exhibit No. 9, that is the declaration of Sandra McLeskey, Ph.D.?
A. Yes.
09:41AM Q. And feel free, of course, to review the declaration.
My question is, is there anything sitting here today that you wish to change or correct in this declaration?
A. No.
(Reading stopped.)
09:41AM MS. PIROZZOLO-MELLOWES: The questioning now continues by Ms. Pensabene and I'll play the part of Ms. Pensabene.
THE COURT: Okay. Well, as long as -- as long as the record is clear who is doing the questioning.
09:41AM So maybe Mr. Rizzi you should do it, so the court reporter knows that when you're speaking, it's Ms. Pensabene.
MR. RIZZI: Of course, Your Honor.
THE COURT: Page 210.
(Deposition read as follows:)
09:42AM Q. Dr. McLeskey, at the time you were doing that research that led to the paper of Exhibit 5, I think it is, was that early in your career as a -- as a researcher?
A. Yes.
Q. Okay. And at that time, were you experienced with
09:42AM dealing with pharmaceutical companies?

A. No.
Q. Was Dr. Kern the head of the lab you worked in at Lombardi Cancer Center at Georgetown?
A. Yes.
09:42AM Q. And was he your boss?
A. Yes.
Q. And what was Dr. -- and was Dr. Lippman the head of the Cancer Center?
A. Yes.
09:42AM Q. And was Dr. Lippman Dr. Kern's boss?
A. Yes.
Q. Back at the time that you were doing this research that we've been talking about, were you familiar with the statements of proposed investigations or forms or material
09:42AM transfer agreements?
A. No.
Q. Okay. Who in the lab at that time would have signed a statement of material -- of proposed investigation or a material transfer agreement with regard to samples with
09:43AM AstraZeneca?
A. It would either have been Dr. Kern or Dr. Lippman.
Q. Okay. You would not have done so?
A. No.
Q. Okay. And at the time, did you -- let me back up.
09:43AM Did you have one way or another -- do you know one way

or another whether there was a statement of proposed investigation or material transfer agreement with AstraZeneca?
A. I did not know.
Q. At the time, did you ever consider whether there was a -- some kind of an agreement or a statement of proposed investigation or material transfer agreement with AstraZeneca regarding samples?
A. I did not.
Q. Why not?
A. It just didn't occur to me.
Q. Okay. When you first called for samples, did you tell Dr. Wakeling that you were calling from Dr. Lippman or Dr. Kern's group?
A. I -- yes -- well, I don't know what I said, but I'm sure I said something like that.
Q. When -- when you first called for samples, did you understand whether Dr. Lippman or Dr. Kern had a preexisting relationship with AstraZeneca?
A. I knew that Dr. Lippman knew.
Q. Now, once you got the preformulated ICI 182,780, was it -- did you understand that its use was restricted to animals?
A. That's all I did was animals.
Q. Could you have used the preformulated ICI 182,780 in people?
A. No.

Q. Could you have sent the preformulated ICI 182,780 to anyone in the public to use?
A. No.
Q. Was it your understanding that the use of the preformulated sample was restricted to use in the Georgetown laboratory in animals?
A. I don't know how to answer that. That was -- that was what I was going to use the drug for.
Q. Well, did you think that -- that you could give it to anyone else to use in research in people?
A. No.
Q. Was the animal work in your laboratory publicly available?
A. Not until it was published.
Q. Could members of the public have access to your laboratory notebooks before they were -- before the paper was published?
A. No.
Q. Did you send the manuscripts or the draft of Exhibit 5 to AstraZeneca anyone at AstraZeneca to review?
A. No.
Q. Was sending the manuscript or draft of Exhibit 5 to AstraZeneca to review have been your responsibility at the time?
A. No.

Q. Okay. When you called to ask for the formulation did you tell anyone at AstraZeneca that you planned to publish the formulation?
A. I said I was preparing a manuscript.
09:45AM Q. Did you ask anyone at AstraZeneca permission to publish the formulation?
A. No.
Q. Okay. I just want to ask a couple of questions about the laboratory notebooks and materials that I know you said you
09:45AM destroyed when you retired. Did AstraZeneca own those laboratory notebooks that you described?
A. No.
Q. Did AstraZeneca have control over those laboratory notebooks?
09:46AM A. No.
Q. Could anyone at AstraZeneca have told you what to do with your laboratory notebooks?
A. No.
Q. When you destroyed the -- threw away the laboratory
09:46AM notebooks, were -- were you aware that the litigation with Teva was over?
A. Yes.
Q. At the time you threw away the laboratory notebooks, did you know about this litigation?
09:46AM A. No.

Q. Did you learn about the litigation after you threw away the notebooks?
A. Yes.
Q. Did you view -- with regard to the two different formulations of ICI 182,780 in your paper, did you view the ICI 182,780 in peanut oil and the preformulated ICI 182,780 as interchangeable?
A. Yes.
Q. In your work did you do any pharmacokinetic analysis of the drugs that you used in the paper at Exhibit 5?
A. No.
Q. Did you do any blood level analysis of the drugs you used in the work that you did in the paper at Exhibit 5?
A. No.
Q. In your work at Exhibit 5 did the ICI 182,780 have any effect on tumor growth or the metastasis of tumors?
A. No.

MR. RIZZI: That's the end of Ms. Pensabene questioning.

THE COURT: Thank you.

(The examination is continued by Ms. Waldron.)

Q. But your testimony is that you believe that AstraZeneca has paid you less than $10,000 to date; is that correct?
A. Correct.
Q. Yeah -- let's -- actually, that's a really good point.

Let me rephrase my question. Do you currently understand that in the late nineties at the time you were doing your postdoc, Dr. Ellis was doing clinical trials related to fulvestrant?

A. I did.

09:47AM Q. When did Dr. Ellis come to Georgetown?

A. I'm not sure, but it was in the late nineties I think.

Q. Did the person who gave you the information about the formulation understand that you were asking in connection with publishing McLeskey 1998?

09:48AM A. I told him that I was preparing the manuscript.

Q. I believe you testified earlier that you believed that your current consultancy with O'Melveny & Myers began in June of 2014; is that correct?

A. Yes.

09:48AM Q. Do you know the date that you signed the agreement with O'Melveny & Myers?

A. No.

Q. Do you know if it was late or early June?

A. It was not early June.

09:48AM Q. Did the consultancy you had with regard to the Teva litigation ever formally expire?

A. I don't know.

Q. Are you aware of being formally released from that agreement?

09:48AM A. No.

Q. Do you have any reason to believe that it didn't continue -- continue on?

A. I'm under the impression that it did not continue.

MS. PIROZZOLO-MELLOWES: That concludes the reading.

09:48AM I'd like to offer into evidence the exhibits that were referenced --

THE COURT: Yes.

MS. PIROZZOLO-MELLOWES: -- in the transcript. They are DTX-545, DTX- 546, DTX-547, DTX- 548, DTX- 22, DTX- 552.

09:49AM THE COURT: Mr. Prugo, any objections?

MR. PRUGO: I'm not sure what all the exhibits are, your Honor, so.....

THE COURT: They are in the binder. So two of them are the subpoenas, I don't know that they have any evidentiary

09:49AM value.

MR. PRUGO: No, I agree.

THE COURT: The other are her declarations and responses.

MR. PRUGO: No problem there, your Honor, that can go

09:49AM into evidence. That's DTX-0552 to -- the McLeskey declaration, sure.

THE COURT: What about DTX-547?

MR. PRUGO: That seems to be another subpoena, your Honor. There is no evidentiary value of the subpoena.

09:50AM THE COURT: Those are the responses and objections.

MR. PRUGO: Well, if the subpoena doesn't go in -- I guess we would maintain the objections. But, frankly, if we haven't objected to the testimony, then I don't really see the relevance of the objection to the subpoena.

09:50AM THE COURT: DTX-547 is not a subpoena.

MR. PRUGO: My apologies, your Honor. No problem with that exhibit.

THE COURT: Okay. So 547 and 552 are in evidence, 545, 546 are not in evidence.

09:50AM And 22 is in, is it not?

MS. PIROZZOLO-MELLOWES: I believe it is.

THE COURT: DTX-22 is in, is it not?

MR. PRUGO: Yeah, that's already in, your Honor. I believe that's already in.

09:50AM MS. PIROZZOLO-MELLOWES: And DTX-548, additional responses.

THE COURT: Yes. Any objection?

MR. PRUGO: Oh, of course not, no.

THE COURT: Okay in evidence.

09:51AM (DEFENDANT EXHIBITS DTX-545, 546 AND 548 WERE RECEIVED IN EVIDENCE)

MS. PIROZZOLO-MELLOWES: That conclude McLeskey.

We would like to read an additional transcript of Dr. Francis Kern.

09:51AM THE COURT: Okay. And are you playing the role Dr.

Kern?

THE COURT: Okay, when everybody is ready.

(THE DEPOSITION OF DR. FRANCIS G. KERN WAS READ BY MS. PIROZZOLO-MELLOWES INTO THE RECORD)

09:52AM MS. PIROZZOLO-MELLOWES:

Q. Could you please state your full name for the record?

A. Francis Gerard Kern.

Q. Where do live?

A. I live in Highland Park, New Jersey.

09:52AM Q. Do you understand that you are under oath today?

A. Yes, I do.

Q. Is there any reason that you cannot provide full and honest testimony today?

A. No, there is not.

09:52AM Q. Would it be okay with you if I call Exhibit 3 "McLeskey 1998?"

A. Fine.

Q. Did Dr. Gellert ask you anything about the samples that your lab received from AstraZeneca?

09:53AM A. I don't know if it was Lisa or Dr. Gellert who answered those -- asked those particular questions. I don't know the direct question that -- that addressed what you have just asked, but I think it became apparent that, yes, it was all about us receiving some samples to accomplish this work.

09:53AM Q. What did you tell Dr. Gellert about your lab's receipt of

the samples from AstraZeneca?
A. That it was 20 years ago, I didn't remember too much about it.
Q. Just to make sure I understand, did I understand you correctly that you only talked to Dr. Gellert one time on the phone?
A. Correct.
Q. Did you ever meet with Dr. Gellert in person?
A. No.
Q. Can you please tell me what your duties are, what's that mean?
A. I am the head of the oncology scouting. We do search and evaluation of any licensing opportunities, partnering opportunities, the academic medical centers to acquisitions of company, biotech companies. So it spans that range, scouting making recommendations as to who should be a partner or who should be -- you know, who we should license from, who we should acquire.
Q. Going back now to Georgetown, approximately how long were you at Georgetown?
A. I left in '97.
Q. Have you ever done any formulation work?
A. Not personally, no.
Q. Do you consider yourself a formulator?
A. No.

Q. I assume this means you have not formulated any parenteral drugs?
A. Personally myself? No.
Q. Did you have access to Dr. McLeskey's laboratory notebooks and data?
09:54AM
A. Access? I guess I could ask to see them if I wanted to, so in that sense I had access, yeah.
Q. Just to be clear, you never had copies of Dr. McLeskey's notebooks or data underlying the McLeskey 1998?
09:55AM
A. No.
Q. When the lab received documentation, say with samples, how would those documents have been kept in your lab?
A. You know, it's hard to say back in 1993, or -- I guess it was just put in a file and put in a file cabinet.
09:55AM
Q. Do you have any specification recollection of your procedures?
A. No.
Q. Who was in charge would you say, was in charge of the day today activities concerning the research that led to McLeskey
09:55AM
1998?
A. I was.
Q. Would you say you directed the research?
A. Yes.
Q. What were your duties as they pertained to the research?
09:55AM
What does it mean to direct the research?

A. You know, you'd meet maybe not daily but at least weekly with Dr. McLeskey, go over the data that had been generated the last week, make suggestions as to what new experiments should be performed.

09:56AM Q. Who came up with the ideas for the research that led to McLeskey 1998?

A. Again, it's a long time ago, so generally I came up with the ideas for the lab, for what was going on in that lab.

Q. How did you decide what drugs you would study or what

09:56AM drugs you would include in the research?

A. Relating to this paper or --

Q. Yeah. Let me take a step back.

How did you decide which drugs you would study in relation to McLeskey 1998?

09:56AM A. We had earlier found that transfection of this particular growth factor, okay, into these breast cancer cells that originally required estrogen for their growth made them resistant to a drug called tamoxifen. Tamoxifen also has what are called estrogenic actions. Even though it functions

09:56AM primarily as antiestrogen, it may -- it has some agnostic effects to the estrogen receptors.

THE COURT: Agonistic.

A. Agonistic effects to the estrogen receptors. Others had shown that growth factors similarly could simulate the type of

09:57AM agonistic effect on a estrogen receptor. We wanted to probe

into the question of whether the mechanism by which this particular growth factor caused this resistance to this drug tamoxifen was through this accentuating the agonistic effects of tamoxifen. So we approached that question by using this
09:57AM pure -- what's called pure antiestrogen, the ICI 182,780, because that causes degradation of the estrogen receptor. So if you could show that the cells could still grow in the absence of estrogen when they had been treated with this drug, that meant that the estrogen receptor was gone, okay, and
09:57AM consequently they had bypassed the need for the estrogen receptor signaling in this particular breast cancer cell.

Follow?

Q. Generally speaking, I think.

A. Okay.

09:58AM Q. So, to hit the highlights, do I understand that you knew that tamoxifen had partial agonist activity?

A. Right.

Q. But ICI 182,780 was a pure antiestrogen?

A. Right.

09:58AM Q. And you new that ICI 182,780 would cause degradation of the receptor?

A. Right.

Q. When did you learn about the resistance of ICI 182,780?

A. Hard to tell. You know, early nineties, probably.

09:58AM Q. To the best of your recollection, how did you find out

about ICI 182,780?
A. I, you know. I knew -- there were a lot of experiments in the literature on precursor to this 162 something, 464, perhaps. Was it 464?
09:58AM Q. That sound right. I'm not sure either.
A. So, you know, there was a lot of publications on that. I don't know how we became aware that that had been replaced, you know, with 182,780. But when we started this work, we wanted to get as close as we could to a drug that would
09:59AM eventually make, or more likely to make its way to the clinic.
Q. When did you start this work? When was the origin?
A. You know, my guess it was probably in 1993. And we published a paper in 1993 showing that tamoxifen resistance in cancer research with FGF 4 transfected breast cancer cells, so
09:59AM it was a continuation of that work. So my guess is 1993, around there.
Q. How did you first procure ICI 182,780 from AstraZeneca?
A. Yeah. I'm not clear on that.
Q. Was there already ICI 182,780 in the lab when you
09:59AM started?
A. I don't think so. You know, others at the Lombardi Cancer Center may have been using it for other experiments. I would assume, you know, that we would have had to request it, the compound, for our particular experiments, you know. But
10:00AM like I said, it was a long time ago. I noticed that Bob Dixon

is an author on this paper. You know, he had much better relations with Alan Wakeling and with the two people who gave us the aromatase inhibitors, you know. It could have been either I requested it or he requested it, you know, but I'm
10:00AM pretty sure that he had to have made that particular request for these particular experiments.

When I moved to Southern Research I did make a separate request to Zeneca, I believe, at the time, you know, and I had to fill out their forms and describe the experiments
10:00AM that I was going to perform at Southern Research. So that's what's making me think we had to do something similar when we were at the Lombardi Cancer Center.

Q. During the telephone call in late August with Ms. Pensabene, AstraZenica's representative, Arthur Mann and
10:01AM yourself, were you asked about whether you had any documents pertaining to McLeskey 1998?

A. I believe so.

Q. What did you say?

A. I said I didn't think so.

10:01AM Q. Did you look for documents at that time?

A. At that time?

Q. Yes.

A. No. I mean, I looked on a few thumb drives that I had around from -- but they were actually from another -- another
10:01AM job, you know. Nothing was on those.

Q. Were you specifically asked to look for documents at that teleconference?
A. I don't recall.
Q. Have you ever before read the subpoena that's marked as Exhibit 2? Have you ever received a request from AstraZeneca or any of AstraZenica's representatives requesting documents related to McLeskey 1998?
A. No.
Q. Have you ever been told by AstraZeneca or any of its representatives not to destroy any documents you had related to McLeskey 1998?
A. No not to destroy? I was never told that, no.
Q. Okay. So you only talked to Dr. Gellert at one time?
A. Right.
Q. Dr. Gellert asked you about your recollection of receiving samples from AstraZeneca?
A. I don't know if it was Dr. Gellert or Lisa.
Q. What did you say on this telephone conference regarding your recollection about receiving samples from AstraZeneca?
A. That we must have received them. I wasn't sure. I think I said at the time I wasn't sure who was responsible at that time.
Q. Did you talk about whether or not you had a confidentiality agreement with AstraZeneca?
A. I believe we did.

Q. Did you have a confidentiality agreement with AstraZeneca in the early nineties?
A. Well, confidentiality or material transfer?
Q. Well, let's start with confidentiality. Did you ever at
10:03AM anytime enter into a confidentiality agreement with AstraZeneca?
A. I don't recall. I don't know.
Q. Well --
A. Material transfer, or whatever, you know, they -- they
10:03AM tend to call it. I don't know.
Q. Okay. Did you ever sign anything titled "confidentiality agreement?"
A. I don't recall doing so.
Q. Do you have any reason to believe -- you have no reason
10:03AM to believe that you did sign a document entitled "confidentiality agreement?"
A. I have no reason to believe that I did not either. So, yeah, I -- I just don't recall.
Q. You currently do not possess any copies of any
10:03AM confidentiality agreements that you signed with AstraZeneca, correct?
A. I do not.
Q. Do you have any documentation indicating that you signed anything called a "confidentiality agreement" with
10:03AM AstraZeneca?

A. I do not.
Q. Now, you've referred to a material transfer form. Did I understand you correctly?
A. Usually It's called a material transfer agreement, an MTA.
Q. Okay. In your words what is an MTA? What are you referring to?
A. You are asking a company for, you know, a portion of a compound that is generally a proprietary compound not publicly available, that you are asking them for a sample to allow you to perform some laboratory experiments.
Q. Can you say with certainty that you signed a material transfer agreement with AstraZeneca in relation to McLeskey 1998?
A. With certainty? No, I can't say with certainty.
Q. You don't currently possess any copies of material transfer agreements that you signed with AstraZeneca in relation to McLeskey 1998, correct?
A. I do not.
Q. I will confess I barely remember where we just left off. I believe you said that you did not have your own personal lab notebooks or data relating to McLeskey 19918; is that right?
A. Um-hum.
Q. And did not copy for yourself Dr. McLeskey's laboratory notebooks or data; is that correct?

A. That's correct.
Q. So, your edits and contributions continued after you left Lombardi Center; is that correct?
A. For this particular paper? Yes.
10:05AM Q. So, McLeskey 1998?
A. Right.
Q. Am I correct then that you would have had some sort of documentation related to McLeskey 1998 with you at SM?
A. It would have been at Southern Research.
10:05AM Q. At Southern Research with you?
A. Maybe an electronic version of the file, yeah.
Q. While you were at Lombardi Center did it have a specification document retention policy?
A. I don't know.
10:05AM Q. You were not made aware of a specific document retention policy while you were at Lombardi?
A. I don't recall whether I was or not.
Q. As you sit here today, you don't recall a particular document retention policy at Lombardi?
10:05AM A. I don't recall one, no.
Q. Do you recall whether or not there were any rules or restrictions on documents that you could take outside of Lombardi, say to your new job?
A. I don't recall there being any, no.
10:06AM Q. Did I understand you correctly that you directed the

research that led to McLeskey 1998, correct?
A. Correct.
Q. And I believe you said that you managed the day-to-day activities; Is that right?
10:06AM A. To the extent possible, yeah, I guess, right.
Q. Were you responsible for designing the studies described in McLeskey 1998?
A. Probably, yes.
Q. Were you the primary individual responsible for actually
10:06AM conducting the research described in McLeskey 1998?
A. No.
Q. Who was?
A. McLeskey -- well, I mean the other authors had contributions but the primary was McLeskey.
10:06AM Q. What was Dr. Sandra McLeskey's role in procuring samples from AstraZeneca relating to McLeskey 19898?
A. I'm not sure she had a role.
Q. Do you have any personal knowledge as to if Dr. Sandra McLeskey procured samples from AstraZeneca related to McLeskey
10:07AM 1998?
A. Personal knowledge? I do not. I mean, you said that I had told her -- or may have told her to go talk to Vose and, I don't know, whoever, Vose and Wakeling, and it's possible that I may have done that, right.
10:07AM Q. As you sit here today do you have a recollection of

instructing Dr. McLeskey to do that?
A. I do not have a specific recollection, but it was 25 years ago.
Q. Do you think it is possible that you told Dr. McLeskey to
10:07AM call Drs. Wakeling and/or Vose?
A. It's possible, yeah.
Q. At the time that McLeskey 1998 was being researched and drafted, could you describe the general process within your group for submitting documents for publication to a journal?
10:07AM A. General process? It depends on who the first author was and their capabilities with English. So Sandra was certainly very capable with English, so she would have written the first manuscript. She would have -- you know, the first draft. I would have read the first draft and would have made editorial
10:08AM changes, content changes, suggestions. Generally it was between the two, first author and a senior author, that would discuss this and then eventually would get to the rest the authors.
Q. In this case those two people would have been Dr.
10:08AM McLeskey and yourself?
A. Right. You know, it's also possible Dr. El-Ashry, who has a very good command of English, would have written the sections of the receptor binding assays.
Q. Did you personally submit a draft of McLeskey 1998 to
10:08AM AstraZeneca before it was publish?

A. I don't have a recollection of doing so.
Q. Do you believe at the time -- did you believe that you needed to submit drafts of McLeskey 1998 to AstraZeneca before it was published?
10:09AM A. Yeah. Now that I think about it, it's usually -- it's typically with MTA that they will want to see the data that's been generated with the compound before publication, so -- but it's quite possible, given the lapse of time that occurred between the time of the manuscript, the material was acquired,
10:09AM who was responsible for acquiring that material and the time when the manuscript was submitted that it just slipped my mind that that was an obligation.
Q. So you have no recollection of telling Dr. McLeskey that she should submit a draft to AstraZeneca; is that right?
10:09AM A. I have no recollection of doing so.
Q. Did anyone from AstraZeneca ever contact you about McLeskey 1998 after it was published?
A. No. Well, beyond the phone call.
Q. In August of 2015?
10:09AM A. Right.
Q. Has anyone from AstraZeneca ever told you that McLeskey 1998 violated any confidentiality provisions with AstraZeneca?
A. No.
Q. Were there ever any penalties or reprimands imposed upon
10:10AM you by AstraZeneca for publishing McLeskey 1998?

A. No. For publishing?
Q. For publishing McLeskey 1998?
A. No.
Q. To your knowledge were there ever any penalties or
10:10AM reprimands imposed upon the Georgetown Lombardi Cancer Center
as a result of publishing McLeskey 1998?
A. Not to my knowledge.
Q. You said that you edited McLeskey 1998 before it was
published, correct?
10:10AM A. Right.
Q. At that time did you have any qualms about publishing the
formulation data in McLeskey 1998?
A. I did not.
Q. Did anyone from AstraZeneca?
10:10AM THE COURT: Mr. Rizzi?
MS. PENSABENE: I'm sorry. I think you just
interrupted the witness.
MS. PIROZZOLO-MELLOWES: I'm sorry.
A. Right. I mean at the time I thought it was probably just
10:10AM something that was a formulation for animal studies.
Q. Did anyone from AstraZeneca ever specifically tell you to
keep the formulation secret?
A. No.
Q. Am I correct that you do not have any documentation
10:11AM showing that you entered into a confidentiality agreement with

AstraZeneca?
A. You are correct.
Q. Am I correct that you do not have any documentation showing that you signed a material transfer agreement for AstraZeneca?
A. You are correct.
Q. Am I correct that you have no paperwork pertaining to the samples you received from AstraZeneca; is that correct?
A. You are correct.
Q. But again, you are not the person that actually procured of the samples that led to McLeskey 1998; is that correct will?
A. I don't know if I was or was not, right.
Q. Do you have any reason to doubt that it was Dr. McLeskey that procured the samples from AstraZeneca?
A. I don't think she procured the samples, it was either myself or Dr. Dixon, right.
Q. So, at the time that the research leading to McLeskey 1998 was being done, you had no knowledge of Dr. McLeskey calling Alan Wakeling; is that correct?
A. I don't recall. You know, I would probably had -- had to have been -- it would have either had to have been myself or Dr. Dixon who signed the forms, right? It could have been we told her, call up Dr. Wakeling and see, you know, if he'll send this to us.

Q. So you are saying if there was a form signed it would not have been Dr. McLeskey?
A. Right.
Q. But do you have any reason to doubt that Dr. McLeskey did call Dr. Wakeling to procure samples of ICI 182,780?
A. I have no personal knowledge that she did, but she could have, yes.
Q. Do you have any reason to doubt that Dr. McLeskey called Dr. Vose for preformulated ICI 182,780?
A. Again, I have no personal knowledge that she did, but it's quite possible that she did.
Q. Did you have any particular restrictions on Dr. McLeskey as far as her communications with AstraZeneca?
A. No.
Q. Did you give Dr. McLeskey any specific instructions regarding the confidentiality or secrecy of the samples received from AstraZeneca?
A. Confidentiality? I'm not sure what you mean by that. Samples aren't confidential.
Q. What do you mean?
A. Well, I mean information is confidential but samples themselves, so I -- I don't quite understand your question.
Q. Did you ever give Dr. McLeskey any specific instructions about keeping her work at Lombardi Center confidential?
A. I don't know if I gave her specific instructions, it's,

you know, sort of implied that you don't publicly announce your work until it's published or ready for presentation.

Q. Did Dr. McLeskey -- let me take a step back. At the time you were doing the research leading to McLeskey 1998, did you know the components of the preformulated ICI 182,780 received from the lab, received from AstraZeneca?

A. No, I don't think so. No. No reason for me to know.

Q. Can you turn to Exhibit 3, which is a copy of McLeskey 1998.

A. The paper?

Q. Yeah. Okay. So in the journal page 698 --

A. Right.

Q. -- which is marked SAN.FUL 641, the second column there's a paragraph headed "drugs."

A. Right.

Q. Do you see that?

A. Yeah.

Q. Seven lines down we see the sentence: For the experiments depicted in Figure 1 B and C 50 mg per mL preformulated drug in a vehicle of 10 percent ethanol, 15 percent benzyl benzoate, 10 percent benzyl alcohol brought to volume with castor oil was supplied my B. M. Vose, AstraZeneca Pharmaceuticals?

A. Right.

Q. Do you see that?

A. Right.
Q. Did I read that correctly?
A. Yes, you did.
Q. Do you know where the information that the preformulated drug, 10 percent ethanol, 15 percent benzyl benzoate and 10 percent benzyl alcohol brought to volume with castor oil --
10:15AM
A. I have no personal knowledge of where that information came from.
You know, at the time I probably assumed it was information that was provided when it was provided to us. That would have been my logical assumption when reading this.
10:15AM
Q. So, am I correct that you did not tell Dr. McLeskey not to publish the details of the formulas, correct?
A. Correct.
Q. At some point we mention the phrase "the research beginning." To the best of your recollection, when did you begin the research that led to McLeskey 1998?
10:15AM
A. Well, like I said, I assume it was following original publications on this kind of -- line of work that appeared in Cancer Research in 1993. So, around that time.
10:15AM
Q. 1993/1994?
A. '92, '93, '94, in that range probably.
Q. Do you think it's possible that your lab received the samples that are discussed on page 698 of McLeskey 1998 in the first quarter of 1993?
10:16AM

A. Do I think it's possible? Yeah, it's possible.
Q. Do you think it's possible that those samples were received by your lab in the second quarter of 1993?
A. You know, I don't -- I don't know. I -- you know, I
10:16AM can't tell if it's first quarter, second quarter. I can't tell if we, you know, ran out of stuff or needed to get more, you know, right.
Q. We've already discussed that on page 698 of McLeskey 1998 it states that preformulated drug in a vehicle of 10 percent
10:16AM ethanol, 15 percent benzyl benzoate and 10 percent benzyl alcohol brought to volume with castor oil was supplied by B. M. Vose.
A. Right.
Q. Do you have any reason to doubt that those particular
10:17AM samples were received by your lab in early 1993?
A. I have no reason to doubt that, no.
Q. Were you aware that it ws AstraZeneca or one of its predecessors that was supplying ICI 182,780?
A. Yeah. One of its predecessors probably at the time.
10:17AM Q. Do you believe that this research was important at that time?
A. Yes.
Q. Why was it important?
A. You know, it showed that growth factors could get around
10:17AM the need for estrogen receptors in a cell line that was

originally dependent on estrogen.
Q. McLeskey 1998 was published in the Journal of Clinical Cancer Research; is that right?
A. Um-hum.
10:17AM Q. To your understanding, who are the people that read the Journal of Clinical Cancer Research?
A. In 1998? So, it's Volume 4, so it was a relatively new journal. People engaged in what's called translational research, I guess you would say.
10:18AM Q. Just so I understand, I guess, the structure with the Lombardi Cancer Center, am I correct that Dr. McLeskey was a postdoc, you were her supervisor and Dr. Lippman was your supervisor in some way?
A. Yeah, I guess you could put it that way.
10:18AM Q. To your knowledge after McLeskey 1998 was published did AstraZeneca ever contact any of your coauthors regarding McLeskey 19698?
A. Not to my knowledge.
Q. Do you have a specific recollection of filling out any
10:18AM particular forms for AstraZeneca before you started your work on McLeskey 1998?
A. No specific recollection.
Q. Dr. Kern, I know we have been talking about samples a lot today, but I know I didn't actually ask you about the receipt
10:18AM of the samples themselves. Were you actually the person that

received the physical samples from AstraZeneca relating to McLeskey 1998?
A. I don't know for certain but it's quite possible I was.
Q. Do you have any recollection of what the packaging looked like for the preformulated ICI 182,780 that was received?
A. No.
Q. Do you recall if there was any documentation that accompanied the samples of the preformulated ICI 182,780?
A. There usually is but, you know, a packing slip at least. Right?
Q. Do you have any specific recollection of what was included with the samples?
A. No.
Q. What is your best recollection of the documentation that was accompanying the preformulated ICI 182,780 samples?
A. My best recollection is no recollection at this point.
Q. So am I correct that you don't know if the Lombardi Center received a certificate of analysis with the preformulated drug samples?
A. Yeah, I don't know. I do not know if they did or not.
Q. Am I correct that you do not know if the Lombardi Center would have received MSDS sheets with the preformulated drug samples?
A. Usually that comes with it, yeah, an MSDS sheet.
Q. An MSDS sheet for each excipient?

A. I don't know. I don't -- I don't know what's on the MSD sheet, yeah.
Q. At the time McLeskey 1998 was published, did you have an understanding of whether those percentages were in
10:20AM weight/volume or volume to volume?
A. Weight/volume or volume to volume, I think they're all liquids, so probably would have been volume to volume.
Q. Do you know one way or the other?
A. I mean, looking at it, I would say they're liquids, so
10:20AM it's volume to volume. I'm not sure about benzyl benzoate, whether that's a liquid or --
Q. Did you test the samples yourself?
A. No.
Q. And as I understand you earlier, that you do not consider
10:21AM yourself a formulator; is that correct?
A. That's correct, right.
Q. Have you had any formulation classes?
A. No.
Q. When vials containing preformulated ICI 182,780 were
10:21AM received at Lombardi Cancer Center, would they have been logged or recorded in some way?
A. I -- I don't know.
Q. And did I understand you correctly earlier that you never talked to anybody at AstraZeneca regarding the components of
10:21AM the preformulated ICI 182,780 received by Lombardi Cancer

Center?
A. That's correct.
Q. And you're not paying for any of the lawyers that are here representing you, right?
10:21AM A. No.
Q. And neither is Daiichi?
A. Not that I know of.
Q. You had referenced earlier, I think, something called an MTA.
10:21AM A. MTA, material transfer agreement.
Q. And I think you referenced one specifically in connection with some work you did at Southern Research -- at SRI, Southern Research Institute?
A. Right, yes.
10:22AM Q. Now, were you referring to a specific MTA that you recall?
A. Yes.
Q. Was that with AstraZeneca?
A. That was. Well, I don't know if it's Zeneca.
10:22AM Q. When I say AstraZeneca, I mean any predecessor.
A. Right.
Q. Have you seen that particular MTA recently?
A. No.
Q. You haven't seen it?
10:22AM A. No.

Q. What made you recall that?
A. Just when the issue came up, I remembered that I did contact Vose in order to get more compound because I needed it to continue the work, once I moved institutions.
10:22AM Q. This was after you had moved to SRI?
A. Right.
Q. So you recalled specifically making a request to Dr. Vose?
A. Right.
10:22AM Q. Has anyone shown you actual -- you an actual material transfer agreement that you entered into with --
A. No.
Q. -- AstraZeneca?
A. No.
10:23AM Q. In that laboratory at that time, in let's just say '93 to '98 time frame, approximately how many other research projects were going on at that time?
A. In?
Q. In your laboratory.
10:23AM A. In my laboratory, four or five, in that range, something like that.
Q. And these were all projects that you were responsible for?
A. Yeah. You know, each postdoc kind of had a project, so
10:23AM yeah.

Q. You may have answered this before, but there was no -- for people who worked in the Cancer Center or in your lab, there was no confidentiality, general confidentiality agreement they had to sign in order to do work in the lab?
10:23AM A. I don't recall, no.
Q. Would you say it was sort of a collaborative environment at the time in terms of sharing --
A. Yes.
Q. -- information with colleagues?
10:24AM A. Yes.
Q. So you would discuss with colleagues projects you were working on, you would share what you were working on?
A. Yeah.
Q. Prior to the research -- sorry, let me back up.
10:24AM Throughout the course of your career, just roughly, on how many occasions do you recall, in connection with research you were doing, making a request for a drug, whether from AstraZeneca or anybody, in order to conduct research?
A. Not too often. A lot of -- I mean, a lot of times, 10:24AM things were commercially available, and that's sort of the first preference, so you don't have to go through that type of paperwork. So, you know, I've had people approach me for cell lines, where we would have to send them Georgetown's MTA.
Q. Okay. Going in the other direction?
10:24AM A. Going in, mostly going in the other direction, yeah.

Q. Okay. Well, so you're saying it wasn't a regular occurrence that you would enter into an MTA in order to obtain a drug for you to conduct research?
A. No, I don't think so, no.
10:25AM You know, we would ask for plasmids. Again, we would have to ask for an MTA for those from other academic laboratories.
Q. Specifically, with regard to McLeskey 1998, I'm not sure the record was clear. Maybe you weren't asked.
10:25AM Approximately for how many years did the research go on?
A. For this particular paper?
Q. Yes.
A. Hard to estimate, but, you know, my guess is it started
10:25AM around '93, '94, in that range, and went to the time that it was finally accepted, which was November, '97, I think.
Q. So you believe that for that entire time, there was research going on towards this?
A. Related to this paper, yeah.
10:26AM Q. And during that time, is it fair to say that you would discuss with colleagues the nature of that research?
A. Yeah, it would be fair to say that.
Q. And you didn't understand that there was any prohibition or restriction on you doing that, did you?
10:26AM A. Not within the Lombardi Cancer Center, certainly, there

was no -- no restriction.
Q. Before the paper was published, in that time frame that the research was going on, did you give any talks or report progress to anyone?
10:26AM A. You know, it's possible some of this work may have been presented at the annual meeting of the AACR as a poster or possibly as a talk. I just don't recall.
Q. Okay.
A. There would be records of abstracts with those people.
10:26AM Q. Approximately what time frame are you talking about?
A. Same time frame. Well, it would be before it was published, yeah.
Q. What is the AACR?
A. American Association of Cancer Research. That's most
10:27AM likely where it would have been presented, if it was.
Q. And is it fair to say that when you undertook to begin a research project at Lombardi, you would do so with the hope and expectation that the work results in a publication?
A. Yes.
10:27AM Q. And that's true with McLeskey 1998?
A. Yes.
Q. Sorry, just going back to relationship with Ms. Pensabene and her first, which is O'Melveny and Meyer, for the record. Is there an actual engagement agreement in place between you
10:27AM and O'Melveny?

A. No.
Q. When did O'Melveny actually start representing you in connection with this case?
A. I think after Arthur -- after the subpoena was delivered,
10:27AM Arthur sent me an e-mail saying that Lisa had offered to represent me, and I think that -- the day after I received the e-mail, the day I received -- I forget which document here -- the request for documents subpoena.
Q. Before that, did you have any reason to believe that you
10:28AM needed counsel in connection with the subpoena?
A. No, I guess not.
Q. Did Mr. Mann explain to you or provide you any information as to why O'Melveny was offering to represent you in this case?
10:28AM A. No.
Q. Going back to the Lombardi Center when you were there. Was there any control on access to the actual facility starting in 1993?
A. Control on access to?
10:28AM Q. To the building.
A. To the building? The doors were locked, yeah.
Q. Well, was --
A. Certainly, the animal facilities were locked up.
Q. Where the animals were?
10:28AM A. Yeah.

Q. So the animals couldn't get out?
A. Well, so other people couldn't get in.
Q. No animals, human or otherwise, okay.
Who actually had access to the lab itself? Did you have to be a employee or somebody working for the Cancer Center to be able to get into the building?
A. Yes. I mean, you know, students could be -- come down because there was -- the faculty at their offices in the proximity of the laboratories.
10:29AM Q. So if you were a student of undergrad or the medical school --
A. We had some undergraduates who were working in the laboratories, right.
Q. Was there some sort of special ID issued to those students so they could get access to the laboratory?
10:29AM A. I don't think so, but I don't recall.
Q. Beyond student ID, was there any other ID that had to be shown to get access to the lab?
A. Yeah, I just don't recall. I'm fairly certain that there were guards there, right. You know, so anybody just coming on and off the street would have difficulty going down into the laboratories.
Q. There was no ID issued by the Cancer Center itself that you needed to get into the Cancer Center lab?
10:30AM A. I don't recall there being so.

Q. Before making the request to AstraZeneca for the samples that were used in McLeskey 1998, did you have any prior dealings with AstraZeneca in terms of requesting samples for a research project?

10:30AM A. No.

Q. And since that time, you referenced the occasion at SRI?

A. Right.

Q. Any others besides that?

A. I don't think so, no.

10:30AM Q. At any time when you working on the project, McLeskey 1998, did you have any understanding that you would not be able to publish the results of the work?

A. No. I mean, I thought I had freedom to publish the work.

Q. During the time you were working on this project, which

10:30AM is described in McLeskey, 1998, did you have any understanding that there was any restriction on publishing the formulation of ICI 182,780 in any publication resulting from the work?

A. Okay. Yeah, I would say if I were -- if I was the one that signed the MTA, I probably would have understood that

10:31AM they wanted to see the paper, the manuscript, before it was submitted, right. That would have been the only limitation that I would have been aware of, right. And I think in there, they usually would have said they're not going to block publication, the publication itself, right, yeah.

10:31AM Q. Okay. So the only -- and, again, you have no

recollection of actually signing anything in connection with this particular project, do you?
A. No.
Q. You're saying hypothetically, if you had, the only restriction you were aware of --
10:31AM
A. I think what I said was it was probably either me or Dickson, we signed that form. If it was Dickson, I might not have been aware of limitation. If it was me, I would have read those terms and, you know, would have been aware of that limitation.
10:32AM
Q. And what terms specifically?
A. You know, usually, there's -- when a company gives you something that's not publicly available yet, they'll ask to see the manuscript before you submit.
Q. And that was the only restriction you might have been aware of?
10:32AM
A. Correct.
Q. Okay. And, again, you have no knowledge that the manuscript or any version of the manuscript was sent to AstraZeneca?
10:32AM
A. I have no knowledge that it was.
Q. Let me ask you this. So, I know you looked at this before and you saw that it was submitted originally --
A. July 3rd.
Q. '97.
10:32AM

A. Yeah.
Q. What's your best understanding as to when a first draft would have been prepared, I believe you said probably by Dr. McLeskey?
10:32AM A. Two to three months previous, probably. That would be my estimate. Could have been earlier, little earlier, in that range.
Q. So, for the work at SRI, you said you do recall there was an MTA.
10:33AM A. Yeah.
Q. And you do recall that the MTA obligated you to provide a manuscript to AstraZeneca.
A. I don't recall that.
Q. You don't recall that?
10:33AM A. No.
Q. So you're not sure if there was an obligation?
A. Not at that time.
Q. But if there was, it didn't happen?
A. Yeah. Somebody screwed up.
10:33AM Q. Was there any other occasion, besides the two we have talked about at Georgetown and SRI, where you received material potentially under an MTA from AstraZeneca?
A. No, I don't think so.
Q. Well, throughout the course of your career, do you have a
10:33AM recollection of any occasion where you sent a draft manuscript

to a drug supplier?
A. Throughout my career? No, I guess not.
Q. Well, wasn't your objective to clearly convey to the research community the work you did; is that fair? That was
10:34AM part of the purpose of the paper, no?
A. That's correct, right.
Q. And the formulation is there, right? So the formulation is there for what it's worth?
A. The formulation is there, right. Somehow or other, we
10:34AM got that information.
Q. And isn't it fair to say that if any of the authors thought that it was important to be more explicit in describing the formulation for purposes of conveying that research, then that would have been done in the paper?
10:34AM A. I -- I'm, you know, fairly certain that we felt we met our obligation for materials and methods section.
Q. And that you had clearly conveyed to the research community what the formulation was?
A. That we had clearly relayed to the research community
10:34AM what the formulation was?
Q. Yes.
A. You know, like I said previously, at the time I didn't really know what a formulation was, to tell you the truth. Okay? So it's -- this is information that was conveyed to us
10:35AM and, you know, that's what we put into the paper.

Q. And you were the one who was ultimately responsible for signing off on the final version of the paper, right?
A. Yeah.
Q. You didn't have any reason to believe when you read it and signed off on the final version -- you read it carefully, didn't you?
A. Yeah.
Q. And you didn't have any reason to believe that there was anything unclear or incomplete about the description of the formulation?
A. I had no reason to believe that.
Q. Sorry. You didn't have any reason to believe that the description of the formulation would in any way prevent researchers in the field from making full use of the results that were -- that you were publishing?
A. No, I didn't have any reason to believe that.

MS. PIROZZOLO-MELLOWES: That concludes Dr. Kern's testimony.
THE COURT: Okay.
(The read in concluded.)
MR. RIZZI: Your Honor, the next witness is a live witness.
THE COURT: Okay.
MS. PETERSON: Dr. Mehta.

THE COURT: Thank you. You may step down.
MR. RIZZI: Can we take a short break?
THE COURT: Yes, why don't we take a five-minute break. Okay?
10:36AM THE DEPUTY CLERK: All rise.
(A recess was taken at 10:36 a.m.)
THE DEPUTY CLERK: All rise.
THE COURT: Okay. Be seated.
MS. PENSABENE: Your Honor, I understand that there
10:53AM was a question about PTX-6, 7 and 8. They are the prosecution histories.
THE COURT: Are they in evidence?
MS. PENSABENE: The parties have agreed that they should be in evidence. Happily, I can say the parties have
10:54AM agreed.
THE COURT: That's nice to hear.
So what are the document numbers? 6, 7, and 8?
MS. PENSABENE: PTX-6, 7, and 8.
THE COURT: Okay.
10:54AM MS. PETERSON: And I think there is a corresponding set of exhibits on JTX-6, 7, and 8 as well. They were produced -- one set was produced by the plaintiff and one set was produced by the defendants.
THE COURT: Yes. So which are the exhibits coming
10:54AM in?

MS. PETERSON: I think we should agree's it's the JTX numbers since that's the joint list.

MS. PENSABENE: That's absolutely fine, Your Honor. They are the certified file histories that come from the Patent Office.

10:54AM

THE COURT: Okay. So JTX-6, 7, and 8 are in evidence.

MS. PENSABENE: Yes. Thank you, your Honor.

THE COURT: Okay.

10:54AM (JOINT EXHIBITS JTX-6, JTX-7, AND JTX-8 WERE RECEIVED IN EVIDENCE.)

THE COURT: Okay.

MS. PETERSON: The defendants call Dr. Mehta to the stand.

10:54AM

THE COURT: Okay. Come forward.

THE DEPUTY CLERK: Good morning.

THE WITNESS: Good morning.

THE DEPUTY CLERK: If you could please take a step in the witness stand, place your left hand on the Bible and raise

10:55AM your right hand.

(DIVYESH MEHTA, HAVING BEEN DULY SWORN/AFFIRMED, TESTIFIED AS FOLLOWS:)

THE WITNESS: I do.

THE DEPUTY CLERK: Can you please state and spell

10:55AM your full name for the record.

THE WITNESS: Divyesh Mehta.
THE DEPUTY CLERK: Will you please spell it.
THE WITNESS: Divyesh, D-I-V-Y-E-S-H, Mehta, M-E-H-T-A.
10:55AM THE DEPUTY CLERK: Thank you.
THE COURT: Okay. Doctor, have a seat, make yourself comfortable.
THE WITNESS: Thank you.
THE COURT: Please speak loudly into the microphone,
10:55AM please. Okay.
MS. PETERSON: May I proceed?
THE COURT: You may.
(DIRECT EXAMINATION OF DIVYESH MEHTA BY MS. PETERSON:)
Q. Good morning.
10:56AM A. Good morning.
Q. Can you please start by introducing yourself to the Court.
A. My name is Dr. Divyesh Mehta. I am a medical oncologist and licensed to practice medicine in the State of Arizona.
10:56AM Q. And do you hold any other titles?
A. I am the chief of oncology services at the Maricopa Integrated Health Services, which is the County Hospital for Phoenix, Arizona.
Q. Anything else?
10:56AM A. I'm also professor of medicine at the University of

Arizona, College of Medicine in Phoenix.

Q. And can you tell us a little bit about your educational background?

A. So I graduated in 1971 from Baroda, India.

10:56AM I came to the United States in 1972. Before that, I had done a year of internship in India and another internship in Chicago, a residency in internal medicine, and then a fellowship at the University of Illinois in Chicago, in hematology and oncology.

10:57AM Q. And are you currently a practicing physician?

A. Yes, I am.

Q. In what areas do you practice?

A. I practice in hematology and oncology, specializing in breast medicine.

10:57AM Q. And you mentioned hematology. What is that?

A. Hematology is diagnosis and treatment of blood diseases, including blood cancer.

Q. And what portion of your clinical practice is devoted to oncology and, in particular, the treatment of breast cancer?

10:57AM A. It has varied over the last 15 years.

While I was in Chicago, from 2003, most all of my clinical practice was breast cancer.

When since coming to Phoenix, Arizona in 2011, 60 percent of what I see are breast cancer; the rest is assorted

10:57AM tumors and some blood conditions which I also see.

Q. And how many breast cancer patients have you treated over the course of your career as a clinician?
A. The number must be in thousands.
Q. And how many patients do you see a month?
10:58AM A. At the moment I see about ten new breast cancer patients a month, and maybe 30 to 50 patients in follow-up or in hormonal or chemotherapy.
Q. And what other prior academic positions have you held?
A. So, I was assistant professor of medicine in -- from late
10:58AM '70s to 1985.

I was associate professor of medicine in Chicago from 2003 to 2011. And during that time, I was also the chair for the Division of Hematology and Oncology at the University of Illinois, and I was also the director of clinical oncology
10:59AM services, which means I ran the chemotherapy services for the University Hospital for the entire program.
Q. And what did you do during the time period from 1985 to 2003?
A. So I returned to India to my hometown, where I graduated
10:59AM from and where I grew up.

I set up a practice as well as I set up three tertiary care hospitals which would provide cancer care. I set up a breast clinic, and I also set up a mammography unit for -- one of the first in Western India.
10:59AM One of the problems we found when we did that was that

most breast cancers came late in India because there were no mammographies, and women would come with a lump that had spread. And so we tried to introduce mammography, and we learned that women were somewhat shy and not really trusting that this would not be photographed or something, and they were worried that there would be man technicians, so we began an education program of why it was important, how it was done. And by that time, we started to educate people to get that done. So that was in the initial part of my return to India.

10:59AM

11:00AM

Besides starting a hormonal and chemotherapy treatment program for breast cancer patients, I was involved in getting diagnostic setups going.

And then I set up ICON.

Q. And what is ICON?

11:00AM

A. So ICON, I-C-O-N, stands for Indian Cooperative Oncology Network. This is a cooperative group, a mentoring group, we set up in Mumbai, and the whole idea was this: There were lots of patients who could benefit from new drugs, but they had no funds to access them.

11:00AM

There were a hundred plus physicians in India treating all kinds of cancer, including breast cancer. They did not know how to put these patients on trials.

And there were drug companies and universities across the world who wanted large number of patients for their trials.

11:01AM

So we became the fulcrum that brought the pharma and the universities to the physicians and the patients.

We also then had to set up education programs, so we set up programs for doctors to be able to do good clinical research, human rights and research, consenting. We focalized what was there, being floated between the drug companies and the doctors, and we monitored it was ethically and transparently carried out.

So this was basically a process that started in mid '90s and now it's in full force. It's become a force that has linked up 300 different institutions in India and covers a population of about 750 million people. So now they have access to modern drugs, and the doctors have access to modern methods of research.

11:01AM Q. And over the course of your career, have you engaged in any clinical research activities associated with the treatment of cancer?

A. So, we just finished a study on impact of HPV in triple negative breast cancer.

11:02AM THE COURT: In what?

THE WITNESS: HPV is an infection that is present on female cervix, and it seems to be responsible for cancer of cervix, certain genital cancers, lung cancer, and ENT cancers, and we had a feeling that it may be linked to the last kind of 11:02AM breast cancer, which is triple negative cancer, the ER

negative, the PR negative, the HER2 negative, the most difficult to treat breast cancer.

And we wondered, there was some evidence in the literature that suggested that it may be related to HPV infection, so we basically studied the last 15 years of our data. The data are basically being presented next month at an oncology meeting.

We also studied --

THE COURT: Doctor, can you slow down just a little?

THE WITNESS: Sure.

THE COURT: Thank you.

THE WITNESS: We also studied breast cancer in Hispanic women and presented two abstracts last year at the San Antonio Breast Cancer Conference which kind of looked at impact of access, impact of insurance, and outcomes. And, obviously, that was of major interest because at County Hospital, we have maybe 30 to 40 percent of women who have no insurance, and we try to give them modern treatment while keeping their financial needs in our sight.

And, of course, I was the part of the team that brought a new molecule called p28. It's a molecule licensed by University of Illinois, and one of the researchers who was working with us. It's a molecule that's a novel molecule, underwent Phase 1 trial, which means we did safety and toxicity and dosing setup trials. The data was presented at

the American Society of Clinical Oncology meeting in Chicago in 2011. And that molecule is now into its Phase II trials.

Q. Thank you.

And have you been involved in any clinical trials for the -- involving endocrine therapy for treatment of breast cancer?

A. So the major one was ATAC trial which compared anastrozole to tamoxifen. And the trial was a national trial, and I enrolled patients on it, and I was the principal investigator for the site of University of Illinois in Chicago. The trial looked at anastrozole versus tamoxifen versus combination.

I also was the principal investigator for Chicago site for a Tailor Rx trial, which basically asked the question if a woman has a early ER cause to breast cancer, do all of them require chemotherapy? And if all of them don't require chemotherapy, some can be simply cured by surgery followed by hormonal treatment alone, how would we detect that these are the patients who can be spared chemotherapy?

And so the trial looked at the genomic makeup of the tumor cell and distinguished who had a high lethal score and would benefit from chemo, and who were slow-growing tumors like turtles that were going to keep going for years and the chemo would really not have any impact on it? So those trial results are just coming out.

And then participated in a Phase III trial looking at avastin versus chemotherapy, a Phase II trial of a new molecule called Epithalone B. It was a negative trial, didn't work in breast cancer.

11:05AM And, of course, as I mentioned, the Phase I for p28.

Q. Have you been involved in any animal research studies over the course of your career?

A. So, during my fellowship at UIC, my boss used to have a lab where we worked. This was a lab that basically worked on

11:06AM mice. And the idea was to look at impact of removing kidneys and how they affected the blood of the -- the animal.

And subsequently during that time of my fellowship, I, along with other trainees, would also look after the dogs who were going through experimental bone-marrow transplants, and

11:06AM we would come in over the weekend and week and basically manage the dogs.

Over the time I was the chair for the oncology program at the University of Illinois, Chicago, I was instrumental in directing the Ph.D.s which were under my division. I would

11:06AM approve their funding. I would approve -- look at the research that is basically going up for further funding. I would look at and mentor them about the animal research that was going on to be published. And my team acted as a liaison between the lab research and what the clinicians wanted the

11:07AM question to be answered in the lab. This was during the

period I was in Chicago.
Q. And over the course of your career, have you presented or published on topics of treatment of breast cancer?
A. Yes. So I have been a speaker all my life and a teacher all my life, the last 15 years, I have addressed physician audiences which sometimes included nurses and pharmacists on breast cancer across United States and abroad, approximately 150 docs on treatment of breast cancer, management of breast cancer, ER positive breast cancer as well as chemotherapy of breast cancer.
Q. And Dr. Mehta, can you please take your binder that's sitting in front of you and turn to the tab that's marked DTX-276. It should be your first binder.
A. Absolutely.
MS. PENSABENE: Counsel, do you have a copy for us?
THE WITNESS: 276? Got it. 276?
THE COURT: It's about the fifth one, tab in.
MS. PETERSON: Is it not in your binder?
THE COURT: It's about the fifth tab in.
THE WITNESS: 276, right? Yeah. Got it.
BY MS. PETERSON:
Q. Sorry for that, Dr. Mehta. Can you identify DTX-276?
A. Yes.
Q. And what is this?
A. It's my copy of my CV.

MS. PETERSON: Your Honor, defendants move to enter DTX-276 into evidence.

THE COURT: Any objection?

MS. PENSABENE: No objection.

11:09AM THE COURT: In evidence.

(DEFENDANT EXHIBIT DTX-276 WAS RECEIVED IN EVIDENCE)

MS. PETERSON: At this point, defendants proffer Dr. Mehta as an expert on the clinical treatment and research of breast cancer.

11:09AM THE COURT: Any objection, any voir dire?

MS. PENSABENE: No, Your Honor.

THE COURT: Okay. Subject to Rule 702, Dr. Mehta will be permitted to testify in the areas identified by counsel as an expert.

11:09AM BY MS. PETERSON:

Q. Now, Dr. Mehta, are you here to testify today about the opinions you have offered concerning invalidity of the patents in suit?

A. Yes.

11:09AM Q. And were all of the facts and data that you considered in forming your opinions in this case disclosed in your expert reports?

A. Yes.

Q. Dr. Mehta, can you just briefly explain for the Court

11:09AM what the primary options are for treating hormonal-dependent

breast cancer?
A. So this is a tumor that is fed and nourished by estrogens, and one of the main strategy was to withdraw estrogen either surgically by removing ovaries or chemically
11:10AM producing menopause. Then the same concept progressed to have agents which would be blocking the estrogen receptors which are like switches on the cells, turning the cells on and egging the cell on for division and -- and of course, all strategy that would reduce circulating estrogen around the
11:10AM cancer cell.
Q. And what types of drugs would fall into the antiestrogen category that you described?
A. So principally, there were three categories. First were the drugs that were selected to be modified, the estrogen
11:10AM receptors were concerned, tamoxifen being the principle example. Other categories were aromatase inhibitors which block the enzyme aromatase and made estrogen non-available to the cell. And the third category where your antiestrogen or estrogen down regulators, ERDs, and the example being
11:11AM Faslodex.
Q. And as of the 1990s, how did clinicians determine what treatment option to use for a patient?
A. Since most of the tumors, since most of the tumors were estrogen receptor positive, the strategy largely had to decide
11:11AM if the estrogen was -- the manipulation was the first

treatment to go to, and if not, if you actually wanted chemotherapy, why.

So as the algorithm on these slides suggest, if you had a life-threatening disease or the patient was extremely
11:12AM symptomatic involving some important vital organ then chemotherapy was fast, it would control the tumor and one would go that route. But otherwise, almost everybody would proceed to options that were listed on the left side of the column where you begin your first line hormonal therapy.

11:12AM Q. Dr. Mehta, were there different options for endocrine therapy available in the 1990s?

A. So if you look at the slide again, talking about the premenopausal versus postmenopausal. In the postmenopausal, tamoxifen was still a major drug which was for the entire
11:12AM decade, sort of dominated the breast cancer therapy. The aromatase inhibitors that arrived and Anastrazole as an example. Megestrol which used the mechanism to block the progesterone receptor was a standard of care if there was tamoxifen failure, and this was an old drug and sort of left
11:13AM over from earlier part of the decade.

And there was also knowledge that if you could block the androgens by just like hetero tested, breast cancer sometimes responded and hetero testing was androgen blocking was an option.

11:13AM On the other end, in the premenopausal, bulk of the

strategies were around tamoxifen or making a woman menopausal. To do -- to put a woman in menopause, the options included a drug that would interrupt the pathway between pituitary and ovary or actually physically taking the ovaries out, so called oophorectomy.

And of course, down the line, the products that were coming were looking at the fact that the post -- the premenopausal woman couldn't be given the aromatase inhibitor if she was made to resemble a postmenopausal woman by using Anastrozole.

Megestrol and androgen, as I had mentioned in the postmenopausal, they were leftovers from earlier part of the decade were still options being used but less and less so.

Q. And just to be clear, looking at your demonstrative up on the screen, DTX-1006, I think you were referring to the treatments for postmenopausal which are on the left side --

A. Right.

Q. -- is that right?

A. Yes.

Q. And then the right-hand side of the screen?

A. Is the premenopausal.

Q. Were other candidate drugs and developments under consideration at that time as well in the late 1990s?

A. So, on one hand, the aromatase inhibitors were already on their way and they were successfully headed for clinical use,

and on the other hand, there were a very powerful group of drugs known as antiestrogens.

Q. Other than the aromatase inhibitors and the pure antiestrogen, were there any other categories of drugs that were under development for hormone-dependent breast cancer?

A. There was more an attempt to also create better tamoxifens. As tamoxifen was a drug that had basically dominated breast cancer care, the question was, could you create a better tamoxifen, higher efficacy or lower side effects, and those were some of the products also being tried.

Q. So out of those three categories of drug candidates, did any of the candidates within those categories appear to be promising as a potential new therapy for hormone-dependent breast cancer at the time?

A. So the prior art during that time identified fulvestrant as a very promising candidate.

Q. Why do you say that?

A. Because there was strong preclinical data suggesting that it was efficacious, it was a novel product, in terms of a new mechanism of action, so it was likely to work when other drugs had failed. The preclinical and clinical data was showing that it did work when tamoxifen had failed. The data also suggested that it being pure antiestrogen had no side effects that would come if we were using tamoxifen, such as endometrial and other changes.

So it had promise in terms of being novel, new mechanism of action, efficacy and safety, and also the prior art was suggesting that this was going to be delivered by a mechanism or a method which would make sure that the patient is compliant and the drug is in, based on the injections.

11:16AM

Q. Now, you mentioned one of the properties of fulvestrant that it had been shown to work when tamoxifen had failed. What's the significance of that?

A. So one of the important lessons of hormonal treatment has been that if you go from one successful treatment to the other, if the next one is effective and not basically negated by prior treatment, you added life and survival to the patient. So as you -- even though one drug fails, you go to the next paradigm and next paradigm and next paradigm.

11:17AM

That's how -- I have had patients who have survived five, ten, 15 years with Stage 4 disease and are doing well because something works and then the cells start to become resistant, something else works. That's what cross-resistant, non-cross-resistant. So not being cross-resistant to tamoxifen was a major attribute here.

11:17AM

Q. And I think you mentioned that fulvestrant was -- or the category that fulvestrant belongs to, the pure antiestrogens, there were no approved drugs within that category, is that right?

A. That is correct.

11:17AM

Q. And what about the other two categories, were there already approved drugs within those two categories?
A. So, the premenopausal group of course had tamoxifen and all of the options of depriving ovarian outputs, such it LHRH
11:18AM antagonists or removal --
THE COURT: Or what? Wait, slow down.
THE WITNESS: LHRH antagonist, the interpreter -- the interrupter of pituitary to ovary access. On the other end, in the postmenopausal group, there were -- one agent was
11:18AM already there, which was a group in Europe and two more were on their way, which was very, very promising.
Q. Now, within the category of the pure antiestrogens, was there any one candidate or -- within that group, that demonstrated more promise than the others?
11:18AM A. I would say that would be fulvestrant.
Q. And why do you say that?
A. The prior art of fulvestrant and the excitement about this being a new novel molecule can be illustrated by this particular slide.
11:19AM Your Honor, the San Antonio Breast Conference is a big pow-wow of breast cancer focused physicians, researchers, even patient care groups arrive and everybody has a way of interacting and learning what's coming new.
So 1999, there were 440 studies presented of all kinds
11:19AM of research on breast cancer of which the most prominent, most

promising 40 abstracts were chosen for a general session, which meant that everybody who came to San Antonio would be likely to attend the general sessions before the sessions break out in smaller rooms. And of those, eight focused on
11:20AM hormonal therapies -- studies. So there were a few of these studies as abstracts presented to this general audience that came from all over the world, including from United States, and of all those studies presented, there was only one new novel product at that time introduced and that was Faslodex.
11:20AM Q. The other seven hormonal therapy studies that were presented at that general session, did those not involve new or novel products?
A. So some of them are comparing tamoxifen to some other methods. Some of them had also talking about aromatase
11:20AM inhibitors. Some had -- but none of them had any product that was not yet in the approval process, and there was excitement about it.

In fact, Dr. Robertson in his presentation on this product was from Dr. Robertson, and he categorized the product
11:21AM as the most advanced pure antiestrogen available in the research community at that time.
Q. If I could actually ask you to turn to the tab marked JTX-13 in your binder. I believe it should be towards the end.

11:21AM Can you identify JTX-13 for the record?

A. Yeah. It covers the abstracts from the general sessions, Page 31.
Q. This is the Robertson abstract that you just referenced in your prior demonstrative?
11:21AM A. Yes.
Q. Marked DDX-10-07?
A. Yes.
Q. And how did Dr. Robertson describe Faslodex in his abstract?
11:22AM A. Simply the first line, he says that Faslodex is the most advanced, of a new class of drugs, a non-agonist, which means a pure steroidal antiestrogen currently in clinical trials in postmenopausal women in the United States, I guess.
MS. PETERSON: Can you go back to JTX-13 first. I
11:22AM think it was asking for the first few sentences.
THE WITNESS: Correct.
MS. PETERSON: Keep going. Yep. Blow that up. Right where it starts, Faslodex.
THE WITNESS: It says, I was seeing the most advanced
11:22AM of the new class of drugs, the non-agonist pure steroidal antiestrogen currently in clinical trials in postmenopausal women with advanced breast cancer.
He was reporting on a randomized, partially blind trial of this particular product in three different dose categories,
11:23AM 50 milligrams, 125 and 250 milligrams in association with

tamoxifen or tamoxifen placebo to see if this drug added any value to tamoxifen and several therapeutic efficacy biomarkers were also measured in that trial.

BY MS. PETERSON:

11:23AM Q. Now, Dr. Mehta, are you familiar with the term a person of ordinary skill in the art?

A. Yes, I am.

Q. And have you provided an opinion as to the characteristics of that -- of that person?

11:23AM A. Yes, I have.

Q. Is it referenced here up on your demonstrative, DDX-10-08? Can you explain?

A. So this person is a hypothetical person but highly educated, having, for example, a Ph.D. or an MB, many years of

11:24AM training and experience in the field of treating hormone-dependent diseases of the breast. This is a person who would understand that the drug development process is a teamwork that requires input from various individuals with various background. For example, a person of ordinary skill

11:24AM in the art would have familiarity with the pharmaceutical formulations or would call on a colleague or a team member for such expertise to collaborate.

Q. And Dr. Mehta, would you consider yourself to have been a person of ordinary skill in the art as of 2000?

11:24AM A. Yes.

Q. Now, prior to 2000, would a person of ordinary skill in the art have been interested in developing a new treatment method with fulvestrant for treating hormone-dependent breast cancer?

11:25AM A. Yes.

Q. And I see you've prepared a demonstrative timeline here, DDX-10-09.

Can you explain?

A. So this looks at a stage of -- stages of drug development

11:25AM for fulvestrant, in terms of preclinical, clinical and some corroborative evidence that came subsequently. For preclinical, 2002, the evidence that then begins to look at actual patient drugs.

Q. And when you said some corroborative evidence that came

11:25AM subsequently, what was the date of those publications?

A. '97, '98, '99.

Q. So they followed the preclinical and clinical studies that you referenced?

A. Yes.

11:25AM Q. But they occurred before 2000, is that right?

A. They did.

Q. Now, who was authoring this literature in the 1990s?

A. So there was a group of physicians and researchers who were very focused on estrogen receptor positive breast cancer.

11:26AM Some of these people were originally being part of the team

that developed tamoxifen, and now we're on to a new product. This is the team -- lot of -- each of these initial studies, the preclinical and clinical had input or team members from the Imperial Chemical Industry, ICI, the team members subsequently Zeneca, AstraZeneca. It was a group that was mentoring and testing a novel compound with a new mechanism of action.

Q. And why is that significant, who these authors were?

A. It sort of -- if you, if you like that work and if these are the people you follow, there is a linear progression of research from their preclinical work which is handed on to clinical work and the same group is now in the corroborative phase talking about the same product.

Q. And where were these results being published?

A. In various, very prestigious journals.

Q. And what was the typical audience for these journals?

A. These were breast cancer clinicians, breast cancer academicians, breast cancer experts, surgeons, pathologists, entire group of doctors who would be interested in treatment of breast cancer.

Q. And let's move on to your next demonstrative, DDX-10-10. Can you -- can you describe this for us?

A. So in a broad overview, we see paper from Wakeling and that basically looked at rational for this product of a pure antiestrogen. The testing was in mice and this was a single

dose given every four weeks.

Moving on to Wakeling further, it was again looking at rational testing in mice and the dose every four weeks. Dukes data was in monkeys, long-acting castor oil formulation. IM injections, 4 milligrams per kilogram every four weeks and then Wakeling and Duke again revisiting the dose and frequency of these treatments in hormone-dependent breast cancer, and again, Dukes '93 going on with further research in the same area.

11:28AM Q. So does this demonstrative, DDX-10-10, does this describe what you were referring to as the preclinical phase?

A. That is correct.

Q. Okay. Well, let's take a look at the first reference on your list. This is Wakeling 1991.

11:28AM Can you tell us actually a little bit about the Wakeling study from 1991?

A. So this study basically looks at fulvestrant and describes it as being a potent and specific inhibitor of estrogen action, and it states that it demonstrated excellent

11:29AM growth suppressive effects in both cells and animals in breast cancer.

Q. And what journal was Wakeling 1991 published in?

A. This was published in Cancer Research.

Q. And who were the authors?

11:29AM A. Dr. Wakeling, Dr. Dukes and Jean Bowler.

Q. And does the article indicate where they worked?
A. They were all part of ICI Pharmaceuticals.
Q. And what results does Wakeling 1991 report?
A. The most relevant part of the study was that this, in a
11:29AM cell line, it compared the new product, fulvestrant, to tamoxifen and on breast cancer cell lines, and it also tried to see one of the criticisms of tamoxifen was that it was stimulating the uterine lining and led to problems, subsequently even endometrial cancer. So it was basically
11:30AM showing an anti-uterotrophic action. So anti means against, utero means uterus, trophic means stimulation of uterine lining. It showed excellent anti-uterotrophic action, and this was achieved without having other side effects of tamoxifen; namely, body weight and impact on gonadotrophic
11:30AM secretion. It was not really working in any other fashion except as a pure antiestrogen.
Q. And these results that you were just referring to, they're described on your demonstrative, DDX-10-12?
A. Yes.
11:30AM Q. And why were these findings important?
A. This established the fact that you have a potent new mechanism of action with a product that can -- in comparison with tamoxifen, have an improved efficacy and without the uncomfortable side effects that you worried about. So you saw
11:31AM improved the efficacy, reduced toxicity. The therapy index

sort of goes up and so it points towards the possibility that this product would have that kind of improved treatment ability.

Q. And what animals were studied in Wakeling 1991?

11:31AM A. So he used MCF-7 cell lines, these are the famous human cell lines that have been nurtured, and are responsible for so many advances in hormone treatment of breast cancer and these were these cell lines on which he tested the first hypothesis, which was the efficacy. He also used rats, and giving this

11:31AM particular product, he also showed that the vaginal cornification, which was one of the changes they described to suggest that there was an estrogenic stimulation of uterus was absent and he also showed in nude mice where he took these -- these MCF-7 cell lines, created a xenograft on the animal and

11:32AM then see -- saw how the fulvestrant acted to see the efficacy.

So I think the -- all three models that he describes, I believe he also worked on monkeys. So the Macaca monkeys, they were basically looking at the same action. He basically demonstrated that if you use fulvestrant, the weight increase

11:32AM of the uterus did not happen, which means the uterus was protected from the uterotrophic action.

THE COURT: Can you just spell what type of monkey you said.

THE WITNESS: Macaca, M-A-C-A-C-A. It's a species

11:33AM they used.

THE COURT: How do you spell it?
THE WITNESS: M-A-C-A-C-A.
BY MS. PETERSON:
Q. Were the animals that Dr. Wakeling studied -- were the animals that were studied in Wakeling 1991, were they ovariectomized?
A. Yes.
Q. What does that mean?
A. It basically means you created a physiological condition, that is, simulating postmenopausal women.
THE COURT: What was the word you said?
MS. PETERSON: Ovariectomized.
THE COURT: Thank you.
BY MS. PETERSON
Q. Dr. Mehta, did Wakeling 1991 teach any information about the preferred method of administration of fulvestrant?
A. So it looked at bioavailability of the drug in all the works in its injectable form, and found this drug to have a very poor bioavailability, and this study also then demonstrated, had a potential efficacy of a depot oil preparation in the nude mouse that were implanted with the xenografts.
Q. And what is a depot formulation?
A. So it's usually a drug given as a -- it's part of an oil depot and depot meaning it sort of stores the drug, releases

it slowly so you have blood levels in a sustained long-term fashion, rather than immediately rising and dissipating themselves.

Q. And why would a depot formulation be desirable?

11:34AM A. In the typical route, it would reduce the frequency of injection, it would also give a very sustained dependable control of tumor. In real-life setting for patients, that basically means that patient would have come less frequently, be monitored with much more efficacy and the problems of

11:35AM compliance that we see with pills would not exist, because we would know the injection is given and it's in there. So if it's working, it's working.

Q. And does Wakeling 1991 demonstrate the frequency of the treatment with the oil depot formulation?

11:35AM A. It was given once every four weeks.

Q. And what does Wakeling 1991 tell a person of skill in the art about using fulvestrant to treat hormone-positive breast cancer?

A. So if you look at the last line of what is put up there,

11:35AM it says that data available for fulvestrant indicate that pure antiestrogens may find a valuable place in treatment of breast cancer. This product will be used to test this proposition. So it kind of carries it forward and offers it for further research to the colleagues as well as their own lab.

11:35AM Q. And you're referring to DDX-10-14?

A. Yes, I am.
Q. Did Wakeling 1991 indicate whether further study with fulvestrant would continue?
A. Yes, it did. The last line again states that this would
11:36AM be used to test this proposition, which means further studies would continue.
Q. Thank you. Let's move on to Wakeling's next publication in 1992. And can you explain what was disclosed in Wakeling 1992?
11:36AM A. Wakeling 1992 was a summary of what his findings were from Wakeling 1991, being presented in sort of a review fashion so that it was a -- his attempt to capsulize what they found, his attempt to also disseminate information so other researchers in the field would also move on with their
11:36AM research with this product, and sort of set the standard of care for what was available, known about this product at that time.
Q. Okay. Let's go on to the next piece of literature, then, Dukes 1992. And in what journal was Dukes 1992 published?
11:37AM A. It was published in the Journal of Endocrinology.
Q. And who were the authors?
A. Authors again were Dr. Dukes, Dr. Miller, Dr. Wakeling again and Waterton.
Q. And would the Journal of Endocrinology be reviewed by
11:37AM breast cancer researchers?

A. Yes, it was a major journal to look at because bulk of breast cancers were endocrine positive, ER positive and lot of endocrine related research was appearing in the journals that were dealing with endocrinology. So it was a major area where these teams were being laid out.

Q. And what does Dukes 1992 indicate to a person of skill in the art who would be interested in developing a treatment for hormone-positive breast cancer?

A. So this study further explored the -- for potency and efficacy of fulvestrant by studying the ovariectomized monkeys and, in fact, on the uterus of these monkeys. They basically used a novel technique which was an MRI scan. So they didn't actually have to weigh the uterus, they would simply estimate the growth of the lining of the uterus by doing sequential MRIs, and this was important study in its own way because it attained sustained blockade effect of estrogen on monkey uterus in a dose-dependent manner for three to six weeks.

He also demonstrated that repeated injections of 4 milligrams per kilogram at four weekly intervals provided an effective blockade for uterine proliferation.

This was an extension of what Dr. Wakeling had suggested, but in a slightly more sophisticated technology. This was confirming what had been seen earlier.

Q. And Dr. Mehta, just for the aid of the court reporters here, if they have a question, if you can just --

A. Absolutely, I'm answering, I'm looking at them, I'm answering. I speed up sometimes and I will slow down and utter each word, no problem.

THE COURT: Was the objective of the Dukes 1992, was it to study the uterine issue?

11:39AM

THE WITNESS: So it basically, yeah, it wanted to study the uterine issue but it also wanted to study the administration, the dose, the injectability. So it wasn't -- Macaca monkey is a larger animal and easier to study than practices for mice, and I think the two things we established here, one was that, yes, he proved again that the uterine simulation was no longer happening with, because of this product, and he showed that this was the way it could happen.

11:40AM

THE COURT: So it seems that it wasn't really related to the treatment of breast cancer, but more so towards --

11:40AM

THE WITNESS: If the treatment was efficacious towards the side effect, right.

THE COURT: Yes.

BY MS. PETERSON:

Q. And what was the significance of the monkeys in the study having been treated with estrogen?

11:40AM

A. And so they were ovariectomized, which means there's a physiological model resembling a postmenopausal woman, and then being given estrogen means that they were challenged with estrogen, but these powerful antiestrogen could block that and

11:40AM

not let the estrogens create increase in the size of the lining of uterus. It would basically prove the hypothesis that this was a product that protected the uterus.

Q. And was your testimony just now, that was a -- just for the record, that was in relation to DDX-10-016?

A. Yes.

Q. And what other results did Dukes 1992 report?

A. So basically, the Dukes, again, from my vantage point, brought the dose of 4 milligrams per kilogram and also showed that there could be a sustained blockade for one month with this dose, and this dosing interval is likely to be clinically relevant in therapeutic studies of breast cancer. This is from the abstract itself, largely because this would translate into monthly visits and monthly injections.

Q. And you're referring to the language on DDX-10-17?

A. Yes, I am.

Q. Can you determine how the 4-milligram per kilogram formulation tested in Dukes 1992 would compare to a dose for breast cancer patients?

A. So, in '90s, when we calculated dose or ordered drugs, the ruling paradigm was, we would say for a 60 to 70 kilogram woman. And if you say 70 kilo, then you're coming to 280 milligrams of dose. If you do 60, then it's slightly less than 250. So it sort of approximates the dose that was to come in future.

Q. And does Dukes 1992 report on the duration of action of fulvestrant?

A. Yes, it does, it says that the blockade continued for four weeks.

11:43AM Q. And how would that four week time period inform a person of skill in the art about the use of fulvestrant for treating breast cancer?

A. It would translate into a depot injection once every month.

11:43AM Q. Let's move on to the next preclinical study from your overview, Wakeling 1993.

Did Wakeling 1993 report on another animal study?

A. He summarized the available state of art at San Antonio Symposium of this new pure antiestrogen that got eventually

11:44AM published in Breast Cancer Research and Treatment.

Q. And what does Wakeling 1993 report?

A. It again goes over these studies we have covered, it looks at the -- can I have the available piece? Okay.

So Wakeling goes on to say that the oil base

11:44AM formulation of fulvestrant in experimental studies in rats showed that the antiestrogen activity could be sustained for long periods with single injection.

Q. And what does Wakeling mention is described about the administration of fulvestrant?

11:44AM A. So it's basically describing an oil depot injection, a

single injection intramuscularly -- single injection at four weekly intervals giving an effective blockade of the same duration, four weeks.

Q. And does Wakeling 1993 provide any information to a person of skill in the art as to what the dose and frequency of administration should be for fulvestrant?

A. So again, as I indicated earlier, a 65, 60, 70 kilo woman, the dose starts to approximate 250 milligrams, it's given in a once a month oil depot injection and it allows you to have a sustained blockade for about a month. So those are the things that are starting to become somewhat clear in the preclinical science.

Q. And this is in reference to your demonstrative DDX-10-19?

A. That is correct.

Q. What does Wakeling 1993 tell the person of skill in the art about the mechanism of action of the fulvestrant?

A. Basically it talks about very powerful antiestrogen reaction of this particular product, which can probably sustain 100 percent blockade of the estrogen receptor. And finally concludes by saying that there is a powerful rationale which argues for the superiority of this particular antiestrogen over other treatments.

THE COURT: Antagonist.

THE WITNESS: Antagonist.

BY MS. PETERSON:

Q. Did Wakeling 1993 provided any teaching as to the sequence in which fulvestrant could be used as a potential endocrine agent for the treatment of hormonal dependent breast cancer?

11:46AM A. It does, because these were oophorectomized patients and the treatment of choice for patients who had relapsed after tamoxifen was becoming an increasingly important subject. So what Wakeling in his particular article surmises is that there's a sound rationale for treating patients who have

11:47AM relapsed on adjuvant tamoxifen therapy with the pure antiestrogens.

Q. And you're referring to DDX-10-21 in connection with your testimony here?

A. Yes, I am.

11:47AM Q. What other conclusions did Wakeling 1993 provide?

A. So summarizing the fact that this was the results that he found impressive for potentially this group of patients, he goes on to say that an initial therapeutic trial has started in patients with advance breast cancer who have failed on

11:47AM tamoxifen.

Q. Let's go to the last of the preclinical publications from your overview. Can you tell me what generally is reported in Dukes 1993?

A. So again, looks at an antiuterotrophic effect of pure

11:48AM antiestrogens on female monkeys with sequential MRI's.

Q. What would a person interested in developing a treatment for hormonal dependent breast cancer take away from this article?

A. So basically it's again validation of the earlier idea that this was an important new mechanism of action. I think the only difference about this particular group was that these were not oophorectomize animals.

Q. And what does that mean?

A. That basically means that this particular physiological system tried to resemble a premenopausal woman.

Q. And what were the results?

A. The results were described as being unpredictable and variable, which means that they did not produce the kind of results one saw in a postmenopausal mortal, these results were not very, very predictable and reliable.

Q. Now, overall looking at all of these preclinical studies, what do they tell a person of ordinary skill in the art looking for new treatments for hormone positive breast cancer?

A. That there was a new agent, that it had a new mechanism of action. That it did not have cross-resistance with the drug in question, tamoxifen. That it was working very well in postmenopausal women. That there was a way of administering it at 4 milligrams per kilogram dose and in an oil based depot injection that could be given for sustained blockade for four weeks.

Q. So let's talk now about your clinical study slides.

What is depicted in this slide as it relates to the clinical studies?

A. So DeFriend basically looked at tolerance, pharmacokinetics, and short term biological effects in women with primary breast cancer. This was a short-acting formulation. They were able to reach plasma levels of 27 nanogram per mL. And was very well tolerated.

Howell, going on from there, established safety in dosing in some owes. Howell went on to look at this in actual patients who had relapsed on tamoxifen. So he looked at pharmacokinetic, as well as therapeutic effects in advance breast cancer. Again, having used a caster oil base injection long-acting. Use 250 milligrams per month. And 13 out of 19 patients responded.

Q. Let's take a closer look at DeFriend 1994.

Can you identify who the authors were of DeFriend 1994?

A. We can see familiar names. Beside that of Dr. DeFriend, we have Anthony Howell, we have Nicholson, we have Mitch Dowsett, we have Dr. Robertson, we have Alan Wakeling, several of the researchers from that time in the UK and several of the team from AstraZeneca.

Q. And what does the fact that these authors were studying fulvestrant, what does that mean to you?

A. These were all very leading authors in their field with

good track records, so they were focused on this product in terms of bringing it to further in its research, the product definitely meriting attention.

Q. Now, how many patients were included in the DeFriend study?

A. So he had a control group of 19 patients and a treatment group of 37 patients, they received daily intramuscular injections of fulvestrant in two dose settings, 6 milligrams and 18 milligrams for seven days and then they were taken for surgery.

Q. And did the study include postmenopausal or premenopausal women?

A. They were only considered for the study if the women were postmenopausal.

Q. And what does DeFriend tell us about how the product was administered?

A. He gave as an intramuscular injection in the buttocks of a short-acting formulation.

Q. And what else does DeFriend tell us about the short-acting formulation?

A. So he gave it for seven days and he used it in two doses, so 6 milligrams versus 18 milligrams, and he was able to measure impact in terms of estrogen receptors, clinical biochemistries, and serum levels of certain hormones.

Q. And what was the dose that was administered?

A. Two kinds of dose, 6 and 18.
Q. I meant the concentration.
A. 20 milligrams per mL.
Q. And what were the results of this trial reported in DeFriend 1994?
A. So one of the things reported were the blood levels he got with the lower dose and the higher dose. And, as you can see in the demonstrative, the higher dose, those levels go all the way up to 25. So when we have 18 milligrams for seven days, the end point seems to be ending at 25 and when we have 6 milligrams for seven days, the end point seems to be under 10.
Q. And is the DeFriend reference you're referring to DDX-10-27?
A. I am.
Q. And does DeFriend report any information concerning the biological activity of the drug?
A. He does. He found --
Q. Go ahead.
A. He found significant reductions in the estrogen receptor levels in estrogen positive tumors in the group both at the 6 milligram level and 18 milligram level but very profound reduction at the 18 milligram level. And the 18 milligram level was statistically very significant, 0.01, and it brought the level down from .73 to .01, which is an extremely low

estrogen level and impressive.

THE COURT: What dose levels, the 6 milligram and --

THE WITNESS: 18.

THE COURT: 18.

11:55AM THE WITNESS: Only those levels, so we have the lowest and highest possibly is there.

BY MS. PETERSON:

Q. Is reduction of receptor expression a measure of efficacy?

11:55AM A. It would translate into efficacy because if you have less receptors, there's less switches to turn on this cancer and its activity.

THE COURT: Can you explain that, please?

THE WITNESS: If you have less receptors -- each

11:56AM receptor is like a switch on a tumor cell and it turns on the electrical, the chemical messages start to go to the cell to divide, multiple, spread, and having less number of estrogen receptors would basically mean that it would be that much less chance for the tumor to progress and grow.

11:56AM BY MS. PETERSON:

Q. Did DeFriend report any information about side effects in the patients?

A. Well, it was a seven day study and they saw no adverse side effects, no patients were withdrawn from the study

11:56AM because of drug toxicity.

Q. What does DeFriend 1994 teach a person of skill in the art who would be interested in developing a treatment for hormone positive breast cancer?

A. So this was a Phase II -- Phase I study in my mind, it looked at the doses, it looked at safety, and it established safety and established some guidelines for doses, and went on to say that this was a new generation of potent pure antiestrogens and is the first therapeutic agent to be investigated in clinical trials with a potential so completely to deprive breast cancer tumors of estrogenic stimulation. And he goes on to say that Phase II trials with a long-acting formulation of this agent are now in progress.

Q. Now, DeFriend 1994 used a short-acting formulation that was administered once a day. Would that be feasible for further clinical studies in humans?

A. In actual patient care that would be absolutely difficult to administer because you cannot expect for months for a woman to have daily injections, so this was impractical. For a presurgical seven day trial it was okay.

Q. Okay. Let's move on to the next piece of literature from your clinical study section.

This is the Howell 1996 article?

A. Yes.

Q. And what type of study was conducted in Howell 1996?

A. It was a pharmacokinetic, pharmacological in studying

antitumor effects of fulvestrant in women with advanced breast cancer.

Q. And do you recognize the authors of Howell 1996?

A. They're all very well known. Dr. Howell, Dr. DeFriend, Dr. Robertson, Sutcliffe, Walton, several from the labs of Zeneca Pharmaceuticals.

Q. Would you refer to this as a Phase II clinical trial?

A. It was.

Q. And what journal is Howell 1996 published in?

A. It was published in the prestigious British Journal of Cancer.

Q. Is that a journal read by breast cancer researchers?

A. Absolutely.

Q. What was the purpose of the study in 1996.

A. So this was the first investigation of an antiestrogen fulvestrant in patients with breast cancer, and the demonstrative that predicted levels of the drug from animal experiments can be achieved and maintained for one month.

THE COURT: Are you saying predicted?

THE WITNESS: Predicted. Right.

Following intramuscular injections of the long-acting formulation.

Can I have the next?

BY MS. PETERSON:

Q. Okay. How was the study designed?

MS. PETERSON: Next slide.

THE WITNESS: So these were again postmenopausal women who had either become refractory to tamoxifen after being given tamoxifen in an adjuvant setting or had disease stabilization and then subsequently progressed and so now they were not responding to tamoxifen.

THE COURT: Schooch the microphone away just a little bit.

THE WITNESS: Yeah.

12:00PM BY MS. PETERSON:

Q. How many patients were in the study?

A. The study, I believe, had -- I'm having a block for a second.

19 patients.

12:00PM Q. And what does Howell say about the dosage that was administered?

A. So they gave a 5 mL depot intramuscular injection, which was a castor oil base vehicle, and he started first five patients at 100 milligrams to make sure there was no new

12:01PM toxicity. And at the end of the month when they did not see that, they upgraded all those patients to the 250 milligram dose and started the new group of patients on 250 milligram dose.

Q. And you're referring to DDX-10-32?

12:01PM A. Yes, I am.

Q. What were the results reported in Howell 1996?
A. So all 19 patients were evaluated, six were unresponsive and 13, 69 percent, responded. And they had a median durational response of 25 months, which was pretty impressive for a Phase II.
Q. Were some of the 13 patients that were designated as responders, did they all show progression or did they all show a partial response to the drug?
A. So I think six of them had stable disease and the rest showed actual shrinkage of tumor.
Q. And would it be typical to categorize results, a new change being an actual response to the drug?
A. So, number one, the group that published this, and we even now basically consider no news is good news, there's no progression in the disease, that means the patient is responding. Because if the patient is not responding, there would be progression and there would be proof of that, so stable disease at this moment is considered a very effective indicator of efficacy. One would obviously hope for shrinkage of tumor evidence. Patients who actually responded were in one category but people who were stable were sort of lumped with people who responded.
Q. So I understand, you're saying the authors categorized the patients who were stable or no change as also being responders to the drug?

A. That is correct.
Q. The reference you're referring to is DDX-10-33, is that right?
A. Yes.
12:03PM Q. What does Howell say about the side effects of the dose that was administered to the patients?
A. No side effects, serious side effects were seen in the 19 patients.
Q. And you are referring to DTX-10-34?
12:03PM A. Yes, I am.
Q. Does Howell make any conclusions with respect to the volume of the drug that was administered?
A. They were all either mLs in the buttock. And again, talking about the side effects there were no local side
12:03PM effects, no pain, no sciatica, no abscesses, things that we worry about with large injections in that site.
Q. What do the authors ultimately conclude about the clinical trial results reported in Howell?
A. So, this is a pure antiestrogen in long term treatment.
12:04PM It seems to be active as an antitumor agent in patients with advanced breast cancer who have relapsed previously on tamoxifen.
Q. And for reference you are referring to DTX-10-35?
A. I am.
12:04PM Q. Now, what is the significance of Howell 1996's conclusion

that fulvestrant is active as an antitumor agent in patients who had previously relapsed on tamoxifen?

A. It tells you that there is no cross-resistance with tamoxifen. People who failed tamoxifen will still respond to this drug. That basically mean it's active in that particular group and something worth exploring.

Q. Let's take a look now, shift to what you had referred to earlier as the corroborative studies, I believe. Turning to the first one in the group, Robinson 1997. What is that?

12:05PM A. So, Robinson 1997 was a study where he took the data from Howell, the patients -- 19 patients and he took his patients, who were on metrozole acetate.

Let me digress and give a little idea of metrozole acetate. So until that point before these other drugs were to 12:05PM arrive on the horizon when people failed on tamoxifen, megestrol acetate was considered to be standard of care second line drug. And so we said okay, if this is the standard second line drug, let's compared it to this new product, is it the same or better or what. But this was not the same trial, 12:06PM these people were not in the same trial, he took Howell's trial, which he was part of, and he took another trial where his be patients failed on megestrol and he compared efficacy.

And he came up with the findings that in case of those who were treating with fulvestrant, the duration of 12:06PM remission, whether they have partial remission or stable

disease, was 26 months. And if you went to the standard of care at that time for failure, which was megestrol, it was 14 months. So it was an almost doubling of the duration. And this -- basically they concluded, this particular study in the paper by saying that these finding support further clinical comparisons between established estrogen therapies and fulvestrant.

Q. What journal was Robinson 1997 published in?

A. The Breast.

Q. And would breast cancer researches in the nineteen nineties have been following that journal?

A. Absolutely.

Q. For reference, you've been referring to DTX-10-37 as part of your testimony just now?

A. Yes, I am.

Q. Now, did Robinson 1997 describe the Howell 1996 in any other way?

A. He goes on to say that a -- number one, he calls it Phase II study, so he's basically looking at efficacy. And he goes onto say rather surprisingly for a second antiestrogen not only did most patients respond, but the median duration was longer than suspected. So they were basically taken by surprise that this drug suddenly was far better than what they were using in clinical practice to treat women who had failed on tamoxifen. Rather surprisingly, it's just their major

comment.
Q. And you are referring to your demonstrative DDX- 10-3?
A. Yes, I am.
Q. In what your opinion, what does Robinson 1997 teach the
12:08PM person of ordinary skill in the art about the use of
fulvestrant to treat hormone positive breast cancer?
A. It basically again confirms that there is an antitumor
efficacy. It confirms that there is -- there are no signs of
agonist activity that one sees with tamoxifen. It sort of
12:08PM sets up the stage for him being able to say that this was a
exciting new product and seems to be working in patients who
have progressed on tamoxifen.
Q. And I think you had explained earlier that this wasn't
actually a real study between two -- between the two drugs,
12:09PM right?
A. So, the classic Phase III study would be randomized where
half would be on one and half would be on the other. The one
would be the standard of care and the other arm would be the
new drug. And then this would then be tested to see if one
12:09PM was better than the other.
He did do a comparison to standard of care, but not
within the umbrella of single trial. He used Howell's
patients and looked at their response and then looked at other
patients that were in his trial on megestrol and compared it.
12:09PM That's called cross-trial comparison and it's used basically

to see if the hypothesis seems to be working.
Q. Now, earlier this week Dr. Robinson testified that there were several questions remaining about the use of fulvestrant to treat hormone positive breast cancer after the results of
12:10PM Howell 1996 were reported. Do you recall his testimony?
A. Yes, I do.
Q. Chris, could you bring up slide number 45 from Dr. Robinson's direct testimony?
THE COURT: Were you here when he testified?
12:10PM THE WITNESS: Yes.
MS. PENSABENE: I'm going to object to this as not having any notice from the defendants that they were going to use this slide with this witness.
MS. PETERSON: Well, it's not one of our
12:10PM demonstratives, it's one your demonstratives.
MS. PENSABENE: Your Honor, the pretrial order is really clear, the demonstratives that are going to be used on direct examination have to be identified prior to the witness. This is a demonstrative, it's being used on direct examination
12:10PM with their witness.
MS. PETERSON: We can do the examination without the demonstrative.
THE COURT: Okay.
BY MS. PETERSON:
12:10PM Q. So, Dr. Mehta, you were here when Dr. Robinson testified

on Monday, right?
A. Yes, I was.
Q. Do you recall Dr. Robinson testifying that there were several questions remaining about the use of fulvestrant to
12:11PM treat a hormone-positive breast cancer, right?
A. Yes.
Q. Did Dr. Robinson reference Howell 1996 containing a group of favorably selected patients? Do you recall that?
A. Yes, he did.
12:11PM Q. Do you agree with Dr. Robinson that that was a concern with the Howell results?
A. I don't.
THE COURT: Was it the patients the 19, were favored?
THE WITNESS: Highly selected group. Highly, that's
12:11PM what he said.
THE COURT: What was the word he used, biased or --
THE WITNESS: Highly selected or, you know, the ones they were probably likely to respond and so subsequently they felt that maybe in a more generic group the similarly
12:11PM responses might not have come. So his words were "highly selected group."
THE COURT: Yes. Do you disagree with him?
THE WITNESS: I do.
THE COURT: Why?
12:11PM THE WITNESS: So, the drug paradigm we were looking

for in this time frame would be postmenopause women that had taken tamoxifen, and that's all these women were. They were highly selected in a way, but yes, they were not triple negative. They are highly selected in the way --

12:12PM THE COURT: They were not what?

THE WITNESS: Triple negative. They were also not ones that had failed other compounds. Like, if this was a second line trial of this drug, it is likely to be quite successful, but not third for people who had not yet been 12:12PM exposed to aromatase inhibitors which were in trial. So, subsequently criticism was that, okay, this is a selected group because you pick patients who had just failed tamoxifen and they were not down the line in terms of lines of therapy. That's what I understand. Nobody has actually in the 12:12PM literature explained what they meant by highly selected.

But the group was basically, by Howell's own admission, postmenopausal women who had progressed on tamoxifen. And these were women who were -- either failed on tamoxifen and progressed or they stopped tamoxifen and then 12:12PM the disease had come back and now they had progressed. So, it's sort of the classic patient where such a drug would be looked for but certainly not a patient who has been failing several lines of treatment where this drug would have been introduced. That's what I think he meant and I think I don't 12:13PM agree.

BY MS. PETERSON:
Q. And do you also recall Dr. Robinson's testimony about Howell 1996's categorization of patients with no change as responders?
12:13PM A. Yes, I do.
Q. Would you have found that to be a clinically relevant finding?
A. I think no change is response. Because in oncology in stage four disease no news is good news. So if a patient does
12:13PM not show progressive tumor and the tumor is stable, achieving stability means you are controlling the growth. So controlling growth is what we are trying to do. And stable patients without symptoms and without anything is good news.
Q. What about tamoxifen withdrawal? What does that refer
12:14PM to?
THE COURT: Can we put up that chart?
MS. PETERSON: Sure.
THE COURT: From Howell?
MS. PETERSON: Oh.
12:14PM THE COURT: Isn't that the chart he's referring to? The responders?
MS. PETERSON: Yeah, sure. That would --
MR. PRUGO: You are referring to Table 2?
THE COURT: Yes. Could I just see it?
12:14PM So, you disagree with how Dr. Robinson broke down the

responders and nonresponders, is that's what you are saying?

THE WITNESS: That's correct. He took away the six with no change saying that should not be counted as responders. But in classic oncology teaching, stable disease in metastatic breast cancer is control. You don't always see shrinkage of tumor, but not growing tumor, not having increasing symptoms basically means that the tumor is under control and you would accept that.

THE COURT: And you would put it under a response category?

THE WITNESS: I would.

THE COURT: Thank you.

BY MS. PETERSON:

Q. Just for clarity as well, the authors of Howell, what category did they put the no change patients in?

A. They put it as part of the 69 percent that responded. So they had bunched it with the responses.

Q. And was Dr. Robinson one of authors on that study?

A. Yes, he was.

Q. Okay. I think we were going to talk next about tamoxifen withdrawal.

A. Yes.

Q. Are you familiar with that term?

A. Yes, I am.

Q. What does that refer to?

A. So, patients who are failing on tamoxifen, there is one small group that is -- actually, tamoxifen is fueling the growth of the tumor because it also has the estrogen stimulating faculties. And it does that. And in that case, 12:16PM if you withdraw tamoxifen, that small group, you will see a short response as the stimulators disappear and then the tumor would start to grow again.

Q. Now, do you agree with Dr. Robinson's conclusions about Howell 1996 and the effect of tamoxifen withdrawal?

12:16PM A. So, I don't think one can quantify it because, again, when you have tamoxifen withdrawal, this is a short-lived phenomenon, can't really use it for therapeutic action. I mean, yes, you can stop tamoxifen, there may be some time during which the tumor may stop progressing, but soon tumor 12:17PM will start to grow again. So I'm not exactly sure how it impacted the numbers. The overall numbers are small, so, again, I'm not sure how much impact it would have had. It's sort of conceptual.

Q. And are you familiar with the term "estrogen 12:17PM sensitivity?"

A. Yes, I am.

Q. Can you explain that?

A. So, to prolong life a woman in stage four breast cancer, as you proceed down the treatment line, first line, second 12:17PM line, third line, it's important that the tumor cells retain

endocrine sensitivity. If the endocrine sensitivity goes way, then the tumor becomes unresponsive.

Q. And do you recall what Dr. Robinson's testimony was regarding the endocrine sensitivity that was reported?

12:17PM A. He was worried that in 10 patients, patients stopped responding to megestrol after the antiestrogen fulvestrant was used and he wondered at that time that -- whether that would mean that if you used fulvestrant would the woman be deprived of any further treatment options.

12:18PM Q. So, was Dr. Robinson -- is the suggestion -- strike that.

Is the suggestion that if you take someone off of fulvestrant that they would become sensitive to all other endocrine therapies?

A. No. The suggestion was that would fulvestrant cause a

12:18PM situation where subsequent treatments would fail. That was his main concern that he voiced.

Q. And the subsequent treatment at issue in Robinson 1997, what drug was that?

A. That was megestrol.

12:18PM Q. And so do you agree necessarily with the hypothesis that the patients who later became insensitive to the megestrol acetate, that would mean that they have demonstrated an endocrine sensitivity profile overall?

A. Again, I don't agree.

12:19PM Q. Why not?

A. So, you already have proven by also prior art that the fulvestrant is a far more powerful agent. And what we are finding on quality is if you use a powerful targeting agent to block a target such as an endocrine receptor, the agents which were of an earlier era, which were much weaker, would now not work. You could only use the most powerful weapon. And if the disease progresses, you cannot go back to drugs which were inferior to that.

THE COURT: Hold on a second.

12:19PM MS. PENSABENE: Your Honor, we've been really patient with this outside the scope, but this is way outside of the scope of the expert reports here.

MS. PETERSON: I think I'm almost done with this. We can move on.

12:19PM MS. PENSABENE: I move to have this testimony stricken, your Honor.

THE COURT: I don't know what's outside the scope. The last answer?

MS. PENSABENE: His whole last answer, this last two

12:19PM answers.

MS. PETERSON: The ones on the endocrine insensitivity.

MS. PENSABENE: This witness never testify about that, never expressed such an opinion in his expert reports.

12:20PM THE COURT: Okay.

Do you agree with that? I mean, unless there is an objection I'm assuming that it's all relevant and within the scope of the expert report. It's much harder for the court to go back and strike testimony because much of it becomes intertwined. So, do you agree that his opinions relating to -- I guess it's the endocrine sensitivity issue, those are all outside the scope?

MS. PETERSON: Well, Dr. Mehta did include the Robinson and discussed the Robinson '97 publication in his expert reports, and in particular the subsequent treatments with megestrol acetate. I don't know if he specifically mentioned the words "endocrine sensitivity" in his report, but he certainly did discuss the Robinson 1997 article and the impact of it.

12:21PM THE COURT: So, the objection goes to the insensitivity to the megestrol acetate? Is that the issue?

MS. PENSABENE: That is correct, your Honor, that was never discussed in --

THE COURT: Okay.

12:21PM MS. PENSABENE: -- Dr. Mehta's report.

THE COURT: So that testimony will not be considered.

MS. PETERSON: And just to confirm, you are talking about the endocrine sensitivity testimony?

THE COURT: Apparently, yes.

12:21PM BY MS. PETERSON:

Q. Okay. Moving on. Are you familiar with the term of an off target effect?
A. Yes, I am.
Q. And do you recall criticism by Dr. Robinson about fulvestrant relative to impacts on other off target tissues?
A. Yes.
Q. What does that mean, this off target effect?
A. If the target is the estrogen receptor positive breast cancer, then all other organs outside that domain would be off target. And what he was referring to was the effect of this particular agent on other organ systems, bones, heart, etcetera.
Q. And had that already been reported in the prior art?
A. There is reference in the prior art where there is a suggestion that there is no impact on bone health.
THE COURT: On what?
THE WITNESS: On bone health.
Q. And when you have potential downsides like that, how does a clinician weigh those in view of the other benefits of the drug?
A. So, all new therapies have obviously some drawbacks. One has to see what you are trying to achieve. If you are trying to achieve efficacy for long life and provide one more mode of bringing the disease in control, and if there were some side effects that did not seem to be as important as controlling

the disease, that would be a tradeoff that one would be able to accept as the therapy index. You have this much of efficacy and you accept this much of toxicity.

Q. In your opinion, would the fact that fulvestrant had been administered as an intramuscular injection in the Howell study, would that have dissuaded a person of skill in the art from continuing work with fulvestrant?

A. No.

Q. Why not?

12:23PM A. Because I think intramuscular is the route that ensures compliance, close physician visits and takes away the chance of patients missing their oral pills. So it's actually a very good way of dealing with a very difficult stage of disease.

Q. And another aspect of Howell was the five mL injections

12:24PM volume. Do you recall that?

A. Yes.

Q. In your opinion, would a 5 mL injection volume, would that have been too large to have been considered as a possible route of administration?

12:24PM A. No. And there were no side effects reported of that.

Q. Are you familiar with the concept of maximum tolerated dose?

A. Yes, I am.

Q. Can you describe what that is?

12:24PM A. So, when you are doing Phase I studies, one of the

objectives is to say what's the maximum tolerated dose, and what kind of toxicities it will produce. And based on the toxicities, a dose is set which is then moved on to Phase II trials to see efficacy. In oncology, sometimes maximum
12:25PM tolerated doses is what you want to use because underdosing can lead to tumor resistance and progression. Underdosing can lead to a tumor line to evolve and get out of control, and then subsequently not respond to even higher doses. So maximum tolerated dose basically insures that you have
12:25PM no emergence of resistance or late emergence of resistance and that's what you want to administer to get maximum benefit for what you are doing.

Q. Is that concept applicable to treatments for breast cancer?

12:25PM A. Yes, it is.

Q. And is it also applicable to treatments -- hormonal therapy treatments?

A. Yes, it is.

Q. Why is that?

12:25PM A. Because for every drug there is a optimum dose. And when you are trying to set a dose, if the evidence suggests, like in Howell it was 250 mg and it was tolerated without major side effects and showed efficacy, I would stay with that dose because in subsequent studies I would not like to tinker with
12:26PM the possibility that the efficacy would drop.

THE COURT: But do you agree that he taught a lower dose?

THE WITNESS: The Howell does say that one should try lower doses, yes.

12:26PM BY MS. PETERSON:

Q. But despite that, did researches, including Howell and Dr. Robinson, continue testing the 250 mg dose?

A. They did. And that went into the Phase III trials.

Q. And the suggestion in Howell that you should be lower

12:26PM than 250 mg, would that have motivated researches to not even look at the 250 mg dose anymore?

A. The most impressive prior art was Howell's one study at 125 and 250, and so why would anybody try to change that? Because you would base your further clinical studies on most

12:27PM effective dose at a Phase II trial.

Q. Does it negate the results that were reported in Howell with that 250 does?

A. It doesn't negate the results.

Q. Was the 250 mg dose in Howell 1996 the maximum tolerated

12:27PM dose for fulvestrant?

MS. PENSABENE: Objection. That's outside the scope of this witness' expert reports.

MS. PETERSON: We disagree. This opinion was disclosed in his reply report.

12:27PM THE COURT: Do I have it?

MS. PETERSON: Paragraph 16.
THE COURT: Do you recall rendering that opinion?
THE WITNESS: Yes, I do.
MS. PETERSON: Would you like a copy?
12:28PM THE COURT: Yes. I don't think I have it up here. Is it in his binder?
MS. PETERSON: It's not in his binder, your Honor.
THE COURT: Okay, thank you.
What was the question that was asked? Was the 250 mg
12:28PM dose in Howell the most tolerated dose for fulvestrant? Is that the question?
MS. MORAN: Maximum tolerated dose.
THE COURT: Excuse me, maximum.
MS. PETERSON: Yes, that was the question.
12:29PM Okay. I'm sorry, your Honor, actually it's paragraph 17 of his report. Would you like a copy? May I approach?
THE COURT: Yes, please.
MS. PENSABENE: Now that counsel submits that, your Honor, I'll withdraw the objection.
12:29PM THE COURT: It seems it was. I'll keep it up here if there is another objection. Thank you.
I think we're going to break it there. Why don't you answer the question and we'll break for lunch.
THE WITNESS: I'm sorry?
12:29PM THE COURT: Continue to answer the question.

THE WITNESS: If I remember the question correctly, was that the maximum tolerated dose or not?

THE COURT: Was the dose that is disclosed in Howell, which what was the 250 mg, was that the maximum tolerated dose of fulvestrant?

12:29PM

THE WITNESS: No. I believe if you consider the DeFriend trials, they had gone with 6 mg versus 18 mg dose. That was given once a day for 7 days. If that was given once a day for 7 days and if you take a 4-week interval where it could be repeated and extrapolate to a 28-day cycle and multiplication of 28 by 18 leads to a dose that is closer to 500 mg. So the dose disclosed in the Phase I trial seems to have no side effects in that particular trial of DeFriend. So, the dose disclosed seems to be around 500 milligrams of fulvestrant.

12:30PM

12:30PM

THE COURT: Okay. We'll leave it at that.

We'll break for lunch. And if counsel many recall, I will see you back at 2 o'clock. Okay? Thank you.

THE DEPUTY CLERK: All rise.

12:30PM

(Luncheon Recess 12:30 p.m.)

THE DEPUTY CLERK: All rise.

THE COURT: Okay. Great. Thank you. You may be seated.

So, my criminal matter has been adjourned, and I thought we would make use of the time. So we'll go about an

01:52PM

hour-ish or so, and then we will take our afternoon break. Okay? So we can continue on.

MS. PETERSON: Actually, your Honor, before we continue, upon further review, we did go back and look at Dr. Mehta's expert reports with respect to the objection about whether he had disclosed testimony concerning the endocrine resistance, and we do think that it was properly disclosed in his reply report, which you do have a copy of in front of you, at Paragraph 15.

01:52PM THE COURT: Did you share it with Ms. Pensabene?

MS. PETERSON: We have not yet.

THE COURT: You didn't talk to her about this?

MS. PETERSON: No.

But in Paragraph 15, he does -- Dr. Mehta does refer to this portion of Robertson 1997 and the possibility of fulvestrant resistance precluding further endocrine treatments as a cause for concern. And then throughout the paragraph, he discusses the benefits and down sides in the analysis that would apply there. So we would ask for a reconsideration of your ruling.

MS. PENSABENE: Your Honor, that is not about this further endocrine insensitivity that's discussed in Robertson 1997. Robertson 1997 is not cited here; nor are the opinions that were provided by Dr. Mehta on further endocrine insensitivity. So I would stand by my objection that this is

not disclosed in his expert report.

THE COURT: So it doesn't seem to be within the scope of what he was testifying to, but I would prefer to have the benefit of the transcript. So were you through with the questioning?

01:53PM

MS. PETERSON: I was through with the questioning, and the witness was through with his answer, as well.

THE COURT: Okay. So there is a motion to reconsider, and I'll reserve.

01:53PM

MS. PETERSON: Okay. Thank you, Your Honor.

Defendants will recall and resume the testimony of Dr. Mehta.

BY MS. PETERSON:

Q. Dr. Mehta, if we could move on to the next publication

01:54PM

discussed in your overview timeline. This would be McLeskey 1998. Can you tell us what journal McLeskey 1998 was published in?

A. *Clinical Cancer Research*.

Q. And tell me about the *Clinical Cancer Research* journal.

01:54PM

Is that something that breast cancer researchers would be interested in?

A. Yes. It is the official journal of the American Association of Cancer Research, and something that sort of is offered just to clinicians, researchers, and people who are

01:54PM

doing bench and animal research. So it's kind of a place

where all research streams come together.
Q. And what was -- and, for the record, Dr. Mehta's testimony here, he is referring to DDX-10-040.
Dr. Mehta, what was the purpose of McLeskey 1998?
01:55PM A. So, McLeskey had a very unique idea. She basically was looking at the MCF-7 cell line, which was until then the most estrogen-sensitive cell LINE for experimentation. She changed it in an -- she changed it in her laboratory, in her lab, and created a cell line.
01:55PM THE COURT: In her laboratory.
THE WITNESS: In her laboratory, and went on to create a cell line that was totally independent, she thought, of endocrine manipulation.
Now, to test her hypothesis, what she needed to do
01:55PM was to try and bring two to three most powerful antiestrogenic agents of that time, and what she chose were three agents that she would test on the cell line and see if it retains its independence, because her further research depended on showing it, because this cell line was not manipulatable by changing
01:56PM anything about the estrogen receptivity.
Q. So, if I could just make sure that we all understand, Dr. McLeskey had taken a -- a cell line that was typically hormone --
A. Sensitive.
01:56PM Q. -- sensitive, and what did she do to it?

A. She changed it in her lab to make it a hormone independent cell line. It's called transfection. And it was basically a application of a growth factor, which then created a cell line that would not respond to hormonal manipulation.

01:56PM Q. And then what was the purpose for which she used the fulvestrant on that cell line?

A. To prove that -- her hypothesis that this was not a hormone manipulative cell line.

Q. And what other compounds did Dr. McLeskey use?

01:56PM A. So she used a -- two aromatase inhibitor and one pure antiestrogen. So she used letrozole, which was then considered to be one of the powerful aromatase inhibitors; she used formestane which, until mid-90s, was proved in Europe and a major aromatase inhibitor; and for the antiestrogen, she

01:57PM chose Faslodex® which was, in her mind, a very powerful new antiestrogen agent.

Q. And, for the record, in your testimony, were you referring to DDX-10-41 and -42?

A. Yes.

01:57PM Q. Does Dr. -- or does McLeskey 1998 describe the formulations of the fulvestrant that were used in this study?

A. She does. She uses two kinds of formulation. One is a -- is a injectable in warm peanut oil, and she uses a second formulation which is a injectable in castor oil. And these

01:58PM are the two things that she basically is using as a source

material for fulvestrant.
Q. And does McLeskey 1998 provide any further description of the composition of the castor oil formulation?
A. Yes, it does. It basically says it was a 50 milligram per mL preformulated drug, in a vehicle of 10 percent ethanol, 15 percent benzyl benzoate, 10 percent benzyl alcohol, and brought to volume with castor oil.
Q. And who supplied the formulation, the castor oil formulation, to Dr. McLeskey?
01:58PM A. This was supplied by Mr. B.M. Vose of AstraZeneca.
Q. And, for the record, Dr. Mehta's testimony -- was your testimony related to DDX-10-043?
A. Yes.
Q. Now, why would McLeskey 1998 be relevant, in your
01:59PM opinion, to a person of skill in the art who would be interested in treating hormone-positive breast cancer?
A. So if you are looking for options in women who had basically progressed on tamoxifen, and the prior art has suggested that there was a powerful new antiestrogen, and you
01:59PM were looking for validation that that was considered to be a new agent with fairly reproducible efficacy, this particular this particular article in this particular experiment goes on to prove that Dr. McLeskey and her group also considered among the three major agents to use to try and prove a hypothesis
01:59PM that they had cell line that were resistant to hormone

manipulation. So, of the three agents she chose, she chose fulvestrant, and this kind of, for me, would, again, reinforce my interest in this product as being something I would be interested in treating ER-positive breast cancer.

02:00PM THE COURT: Could you try that again?

THE WITNESS: So, I think this particular piece of art identifies and sort of says, okay, if you were to choose the most interesting and powerful agents of that time to test the hypothesis that we have a cell line that if we try to 02:00PM manipulate with a hormonal treatment, it will still remain independent, because there is a theory that you must eventually develop a cell line that is completely hormone independent. Eventually ER-positive cancer requires chemotherapy because the hormonal manipulations eventually 02:00PM fail to do anything. And even then, they are basically moving on to chemo when tamoxifen and subsequent drugs fail. So this -- basically, she -- her hypothesis was that these cells are independent because there is another pathway in progress.

And so, if the estrogen manipulation blocks one 02:01PM pathway, the cancer cells find a way and keep growing because they are being driven by a different pathway. So when they start to grow, the tumor grows, and now, manipulating estrogen receptor by any kind of pharmacological agent would not lead to any kind of efficacy.

02:01PM And, to prove that point, she selected three major

agents of that time. One was letrozole, which was a very powerful aromatase inhibitor. Another was formestane. And what antiestrogen did she choose? Fulvestrant. And all three failed to affect her independent cell line, proving her point that she had an independent cell line. But point for me of interest is that she picked fulvestrant as one of the three.

MS. PETERSON: Maybe I could ask a few follow-up questions to maybe clarify.

THE COURT: Okay.

BY MS. PETERSON:

Q. So would you expect an antiestrogen like fulvestrant to block the tumor activity in an estrogen-dependent cell line?

A. Yes.

Q. Now, would you expect an antiestrogen like fulvestrant to block the tumor activity in an estrogen-independent cell line?

A. No.

Q. Now, had Dr. McLeskey created an estrogen-independent cell line?

A. That is correct.

Q. What was she trying to prove?

A. That it was estrogen independent.

Q. And so was she trying to prove a hypothesis that -- or strike that.

So what was she using the fulvestrant for as part of that hypothesis?

A. So she was basically saying a fulvestrant, which is a powerful antiestrogen, cannot stop the growth of this particular cell line, and so it's not affected by it, proving its independence from that agent.

02:03PM THE COURT: But it was a hormone-independent cell line.

THE WITNESS: Right. She had to prove that point before she went on with the cell line.

THE COURT: So if you were interested in treating a 02:03PM hormone-dependent breast cancer, what would McLeskey say to you?

THE WITNESS: Basically, again, all it would say to you is that among the three agents she chose, of her time, which was considered very powerful to test this hypothesis, 02:03PM Faslodex® had made the grade, and so it must have been impressive enough for ICI, AstraZeneca to supply, from the other side, but not to supply the letrozole, and, of course, fulvestrant -- the formestane is the third aromatase inhibitor already in the market in Europe, so they are using that as a 02:03PM third agent to see. Because these are all again -- the hypothesis is that if this cell line indeed is independent, these three powerful agents, none of them will show that the growth of the cell line will slow down. And that's what she was wanting to show, and that's what she ended up showing.

02:04PM Q. So would a person of skill in the art reading McLeskey

understand that ICI 182,780 was chosen because it was recognized to be an effective antiestrogen?

A. Chosen because it was novel and a powerful antiestrogen, yes.

02:04PM Q. And did she prove her hypothesis?

A. She did.

Q. So does that mean that McLeskey's study was actually a success?

A. From the viewpoint of what she was trying to prove, yes.

02:04PM Q. And so do you consider McLeskey 1998 to represent a treatment failure, in your opinion?

A. No.

THE COURT: Were you here for Dr. Kern's testimony?

THE WITNESS: Yes. No. I was here for

02:05PM Dr. Robertson.

THE COURT: Were you here this morning for Dr. Kern's?

THE WITNESS: No.

BY MS. PETERSON:

02:05PM Q. So would a person -- a person of skill in the art interested in using fulvestrant to treat hormone-positive breast cancer, what would such a person learn from McLeskey?

A. That if you are looking for a new powerful agent in the antiestrogen category, you had an interesting agent that

02:05PM deserved attention and further studies.

Q. And what would a person of skill in the art understand from McLeskey with respect to the castor oil-based formulation?

A. So, McLeskey follows Howell, and Howell talks about a castor oil formulation. And McLeskey gives that formulation with the other fill-in-the-blanks agents. And it's around the same time that Howell's results are published, subsequently comes McLeskey, and to me, it would suggest that if I see ICI or AstraZeneca supplied Dr. Howell his product, then the same product was in McLeskey's article, and so that's the formula of fulvestrant at that time in use.

Q. And did McLeskey 1998 cite to and reference the Howell 1996 study?

A. She does. One of the references she cites is exactly that article, Reference 19.

Q. And you are referring to your demonstrative, DDX-10-044?

A. Yes.

Q. Is there anything in McLeskey 1998 that would have dissuaded a person of skill in the art from pursuing a long-acting, 50 milligram per milliliter, castor oil-based fulvestrant formulation to treat hormone-dependent breast cancer?

A. No.

Q. Let's move on to the last publication from your overview. This would be the Robertson 1999 abstract.

And can you just briefly tell us again what does the Robertson '99 abstract teach?

A. So these are the postmenopausal women. These were being scheduled for surgery, and before surgery, a treatment protocol was given. The women were given fulvestrant dose of 50 or 125 or 250 intramuscularly, with tamoxifen in one group, and in the comparator group tamoxifen placebo. And his idea was to -- that group's idea was to test this -- and he calls it the most advanced of the new class of drugs. In this particular two category, you see what happens.

Q. And is this the same abstract you identified earlier in your testimony?

A. This is the same abstract that was presented to the preliminary session of the San Antonio Breast Conference in 1999, selected out of 440 abstracts presented at that particular conference.

Q. And what does Robertson 1999 say about fulvestrant relative to other pure antiestrogens under development at the time?

A. He goes on to call it the most advanced of the new class of drugs, a non-agonist, and to quote, "pure," steroidal antiestrogen.

Q. Before we move off this topic of all the prior art, I do want to go back and follow up on one point.

A lot of -- do you recall a lot of the papers you had

discussed involved research discussing anti-utertropic effects of fulvestrant?

A. Yes.

Q. Why would that be relevant to a breast cancer researcher looking for a new treatment?

A. So, think of what was prevalent at that time. The most important drug at that time was tamoxifen. And while it was very useful in most of the women, where it created problems was that it was not a pure estrogen blocker. In some instances it stimulated like a estrogen.

And the one other it stimulated was uterus. It would increase the uterine lining. There are problems with menorrhagia and excessive blood loss.

And the worst of it was that in a small number of women, the incidence of the lining of the uterus cancer going up was noted.

So one of the ways you start looking at a drug is to say is it efficacious, and the prior art shows in the earlier preclinical phase that on the cell line, in the xenograft, there was efficacy.

But, simultaneously, the second question that was equally important was: Does it have any advantage in terms of side effects? And it came up with this not have it being a very strong anti-uterotropic agent, which basically meant that it did not have the attribute to stimulate the lining of

uterus, and thereby, it was possible that the side effect of uterine cancer could be prevented.

So you have a drug that has a promise of efficacy and a promise of not having the side effects of the prevailing main agent you are trying to find an alternative. And that's probably the way this science then progressed.

02:10PM

MS. PETERSON: Your Honor, before we move into the next area of Dr. Mehta's testimony, I would like to move into evidence the exhibits that he has discussed thus far. The defendants move to enter PTX-392, DTX-285, JTX-13, DTX-39, DTX-48, JTX-16, DTX-49, JTX-17, JTX-15, JTX-11, JTX-14, and JTX-10.

02:11PM

THE COURT: Okay. Any objections?

MS. PENSABENE: No objection, your Honor.

02:11PM

THE COURT: Okay. In evidence.

(DEFENDANT EXHIBITS' PTX-392, DTX-285, JTX-13, DTX-39, DTX-48, JTX-16, DTX-49, JTX-17, JTX-15, JTX-11, JTX-14, and JTX-10 WERE RECEIVED IN EVIDENCE.)

BY MS. PETERSON:

02:11PM

Q. Dr. Mehta, in your opinion, would a person of ordinary skill in the art have been motivated to select fulvestrant to treat hormonal dependent breast cancer?

A. Yes.

Q. Why?

02:11PM

A. Because the prior art had a sort of seamless transition

from preclinical studies showing efficacy, safety, tolerability, a definite method of administering it, which would create a sustained drug level and require less frequent administration, and the Phase I trial showed that it was safe, and the Phase II trial again confirmed in human beings that it was really efficacious. And so all that would basically bring us to the corroborative pieces again, with Dr. Robertson and other articles, that basically at that time heralded this drug as the most advanced of the antiestrogen, and that would certainly make it a very interesting subject to pursue.

Q. And, in your opinion, would a person of ordinary skill in the art have been motivated to select fulvestrant to treat hormonal dependent breast cancer over candidates in other categories of antiestrogens?

A. So the candidates in other category were already moving on. If you had a postmenopausal woman and the development was for aromatase inhibitors, three agents are already on their way to approval.

In case of the SERMs, the category where tamoxifen was the principal agent, there were attempts to develop better tamoxifen or safer tamoxifen, except really no agent came to surpass or better the level of tamoxifen.

In some of them, which were similar to tamoxifen, but not really efficacious, but they were found to have better side-effect profile, and moved on to get approved for

something like preventing osteoporosis like Raloxifene.

But in the third category of pure antiestrogen, which was a novel mechanism category, the most promising compound was fulvestrant. And somebody who is interested in developing something at that stage would say, okay, I realize they are on their way to approval and are already doing very well. Tamoxifen is the centerpiece of this particular mechanism. This is interesting because a different mechanism, not likely to be cross-resistant, and I'm interested. And the prior art would lead you then to develop that further.

Q. In your opinion, would a person of ordinary skill in the art have been motivated to develop a long-acting fulvestrant-based breast cancer therapy before 2000?

A. Yes.

MS. PETERSON: Chris, if you could pull back up again Dr. Mehta's demonstrative DDX-10-09.

BY MS. PETERSON:

Q. So, if you could just explain your opinion.

A. So, basically, that is a seamless transition in terms of time and evidence. The Wakeling and Dukes data tells us that on cell lines of MCF-7, this product was efficacious.

It tells us that on rats and monkeys, the side effect of stimulating uterine lining was not present.

It takes us to a Phase I study in DeFriend where before surgery, given every day for seven days, the product was seen

to be safe and had efficacy in terms of reducing estrogen receptors.

In Howell, in Phase II, it proved that it was efficacious in actual patients who have resistance to tamoxifen, were postmenopausal, and produced 69 percent improvement in a fairly impressive duration of response.

And, to go on, if that evidence is not enough, there were evidence and praise coming in from some of the principal authors of the preceding papers who were now saying this is the most advanced of the antiestrogens. And they were already trying it in their own patients for further trials with standard of care, megestrol, or further trials where they were saying preoperatively, let's look at the product, plus tamoxifen which is a product, plus placebo, and see where we go.

So not only did it impress these investigators, but they are proceeding with further studies and clinical studies which were on their way to Phase III trials.

Q. And, in your opinion, would a person of ordinary skill in the art have had a reasonable expectation of success that a fulvestrant formulation would work to treat hormonal dependent breast cancer?

A. Yes.

Again, same argument. The preclinical, clinical studies progressed in a logical lockstep, and come to Howell,

where you see the efficacy of 69 percent in this population, which was resistant to tamoxifen, and you have other evidence that suggests that it will basically be a product of promise.

Q. And would your opinion be the same for a person of ordinary skill in the art having a reasonable expectation of success that a castor oil-based formulation would work to treat hormonal dependent breast cancer?

A. So Howell used a castor oil-based formulation once every month and showed his results, and, yes, I would expect that to be the principal formulation of interest.

Q. And what does the teaching of McLeskey 1998 add to your opinion?

A. It basically tells me that that group also considered Faslodex® as a principal representative of the antiestrogens to test their hypothesis that the estrogen therapies do not work in that independent cell line.

THE COURT: Which would be more valuable to someone who was looking for a treatment for hormonal independent breast cancer, correct?

THE WITNESS: That, and if somebody was saying, okay, I have enough evidence about fulvestrant that it seems interesting from Howell, here was another proof that another group of investigators chose that drug to test their hypothesis that such a powerful drug would not modulate this cell line. So it sort of identifies and stamps the product

with approval from another set of investigators.

And McLeskey was not part of the AstraZeneca ICI complex. She was an independent investigator. So her group, having brought this product for their experiment, sort of created one more impression which, in my mind, is corroborative, saying okay, it's a front runner with letrozole and with the formestane, that this is the product she chose. So even though the cell lines didn't respond to them, they were not supposed to. The fact that she chose that, it basically tells you that she also evaluated the prior art that was assisting them and said, okay, of the antiestrogens, I'm going to use this to prove my hypothesis.

THE COURT: When you said earlier that it was not a treatment failure, is that what you meant?

THE WITNESS: I meant that it is not a treatment failure because she was not looking for treating estrogen-positive breast cancer.

Her study had a hypothesis that these are independent cell lines, and she was successful in proving it. And so it's a positive study. She would report as a positive study. And you can't go and say it's a treatment failure because she wasn't treating estrogen-positive hormone cancer.

THE COURT: So let me see if I can summarize what you're saying. It was a success, her study was a success because it proved her hypothesis that the line that she was

developing was hormonally independent.

THE WITNESS: Right.

THE COURT: And she proved that hypothesis by treating it with Faslodex® and powerful, to use your word, antiestrogen.

02:19PM

THE WITNESS: Yes.

THE COURT: But it did not deal with treating the disease itself.

THE WITNESS: No.

02:20PM

THE COURT: Okay. Thank you.

BY MS. PETERSON:

Q. Dr. Mehta, just to make the record clear, the hypothesis that Dr. McLeskey was teaching, did that relate to a method of treatment or was it just -- or was it related to establishing

02:20PM

whether a cell line was independent?

A. So I think what it basically established is that this powerful product would not have any effect on her independent cell line, but the fact that she used that particular formulation means that she thought that if she had to test

02:20PM

with the best working formulation of that time, that the AstraZeneca supplied, then she would use the formulation that had shown success in Howell which came before her. So why would she use something else?

Q. Was it unexpected that an antiestrogen like fulvestrant

02:21PM

would not work on her estrogen-independent cell line?

A. So, if it was truly independent, then it should not work.
Q. And that's why she successfully proved her hypothesis?
A. She did.
Q. Do you recall Dr. Robertson's testimony about several hormonal therapies from the 1990s that failed to receive approval?
A. Yes, I do.
Q. In your opinion, does the fact that a drug fails to receive FDA approval indicate that it was not efficacious?
02:21PM A. No.
Q. Why not?
A. Because so many drugs don't reach FDA approval. Some are effective but may not complete all the trials. Some, the pharmaceutical industry that's sponsoring it may lose
02:21PM interest. There are a lot of products that don't complete the entire journey, but they may be otherwise quite relevant.
Q. Now, Dr. Mehta, you're familiar with the patents-in-suit, right?
A. Yes.
02:22PM Q. Can we put up demonstrative DDX-10-46.
Do you recognize this claim from the '122 patent, generally representative of the claims asserted in this case?
A. Yes, I do.
MS. PENSABENE: Your Honor, this claim is not at
02:22PM issue in this case.

THE COURT: Okay.

MS. PETERSON: I'm only trying to establish --

THE COURT: Background?

MS. PETERSON: Yes, just background. I'm only trying to establish what elements of the claim, in general, Dr. Mehta's testifying to.

02:22PM

MS. PENSABENE: Your Honor, it's not representative. The assertion that's being made is that this claim is representative of the claims at issue in this case and that's just not true.

02:23PM

MS. PETERSON: And, your Honor, we provided notice of this demonstrative to AstraZeneca I think two days ago, and they did not indicate that they had any objection to us using it. We could have prepared a different demonstrative using one of the asserted claims. But --

02:23PM

THE COURT: What is the question? Let me hear the question.

BY MS. PETERSON:

Q. Within these claim elements, which portion are you opining on?

02:23PM

A. Method of treatment.

THE COURT: "Method of treatment" he said. Okay.

MS. PETERSON: And that's it.

THE COURT: Okay. Are you going to show him the relevant claim?

02:23PM

MS. PETERSON: I can, sure.

THE COURT: Okay.

BY MS. PETERSON:

Q. Can you pull up JTX-1? Actually, pull up JTX-4, please. Go to the claims. If you could go in on -- go to Claim 1, which is the original independent claim on which one of the asserted claims-in-suit depends from.

Dr. Mehta, looking at Claim 1, can you tell me what element of the claim you're primarily opining on?

A. The one where it says the method for treating hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such a treatment a formulation comprising of 50 milligrams of fulvestrant, and then the description of ethanol benzyl alcohol, benzyl benzoate, and sufficient amount of castor oil vehicle.

Q. Okay. And you just read the entire claim.

A. Right.

Q. I was just asking you which portion of the claim are you opining on?

A. The method.

Q. And then if we could go down to Claim 10 now.

THE COURT: Ms. Peterson, if you want to use your prior chart, that's fine. I just didn't know if you were going to get to it but -- what was the number?

MS. PETERSON: The demonstrative?
THE COURT: Yes.
MS. PETERSON: It was Number 46.
THE COURT: Yes, I don't see any harm in using it.
02:26PM BY MS. PETERSON:
Q. Dr. Mehta, you're not -- oh, excuse me.
THE COURT: Yes, okay. Go ahead.
BY MS. PETERSON:
Q. So you're primarily responding -- you're primarily
02:26PM opining on the method-of-treatment aspects of the claims, right?
A. Yes.
Q. Are you offering opinions as to the formulation or pharmacokinetic aspects of the claims?
02:26PM A. No, I am not.
Q. Okay. You could take that down.
If you could pull back up Demonstrative Number 47.
Dr. Mehta, can you summarize for us the patient populations and animal models that were used in the studies of
02:26PM fulvestrant that you described earlier today?
A. So, all the studies except one basically looked at either ovariectomized animal systems or postmenopausal women.
Q. And, again, what are the ovariectomized animals?
A. So they are the physiological model for a postmenopausal
02:27PM woman.

Q. And is there a study in this group of studies that is a different patient population?
A. So Dukes 93 had intact ovaries and similar testing to other hypothesis was done.
02:27PM Q. And what does that patient population represent?
A. So, that patient population refers to the premenopausal women.
Q. Now, do the postmenopausal women and ovariectomized animal populations in your demonstrative reflect the
02:27PM indication for which Faslodex® was originally approved to treat?
A. Yes.
Q. Now, switching back to the patents in the case, you have reviewed the specification of the patents?
02:28PM A. Yes.
Q. And, in your opinion, does the specification of the patents-in-suit inform a person of ordinary skill in the art that the inventors were in possession of a method for treating hormonal dependent breast cancer in premenopausal women?
02:28PM A. No.
Q. Why not?
A. Because there's no data. The data that you have on the chart there, the only particular group that even simulates the premenopausal women were Dukes 93, and there the outcome was
02:28PM that the -- when the drug was used, the results were variable

and unpredictable, so really you can't translate that into clinical efficacy in any way.

Q. Limiting your analysis just to the patent, does the specification of the patent inform a person of skill in the art that the inventors were in possession of a method for treating hormonal dependent breast cancer in premenopausal women?

A. No.

Q. Why not?

A. There is no -- no evidence or data supporting that contention.

Q. There is no evidence or data supporting that contention where?

A. In these patients.

Q. Do you agree or disagree that once a scientific rationale for a drug has been demonstrated in postmenopausal women, that could be applied to premenopausal women? Do you agree with that?

A. No, I don't.

Q. Why not?

A. These are two different models in terms of what's happening in their systems.

The premenopausal hormonal system is a tsunami of estrogen hormone. So throughout the menstrual periods, the estrogens rise and fall; throughout lactation, they rise and

fall; throughout pregnancies, there is a very sustained surge, and the ovaries produce a very large number of -- amount of estrogen.

Compared to that, in a postmenopausal woman, the ovaries are gone. In terms of functionality, estrogen levels have dropped. Slowly, the ovarian function is starting to diminish to the point where all of the menopausal symptoms and signs are taking over.

And these two -- these two models are -- when breast cancer happens have totally different applicability.

So, for example, a postmenopausal woman will respond even to a tiny amount of estrogen, that is converted from androgen by enzyme aromatase.

But in the case of premenopausal woman, these surges of estrogen are high, and hence, the same system, same idea of control, does not usually work.

So these are -- for all the times we have treated them, the premenopausal milieu, M-I-L-I-E-U, is a totally different entity, and has different efficacy for different drugs.

02:31PM Q. Now, in your opinion, could a person of ordinary skill in the art use fulvestrant to treat hormonal dependent breast cancer in premenopausal women without undue experimentation?

A. No.

Q. Why not?

02:31PM A. Because, again, there is no data to suggest how it is to

be used or whether it will be useful, and so it would require a new experimentation to prove that point.

Q. Does the patent provide any examples of how to treat premenopausal women?

02:31PM A. No, it does not.

Q. And what does the prior art say about treating premenopausal women with hormone dependent breast cancer?

A. Until that time, nothing. And the only report that we have is from Dukes 93, which sort of suggests that it probably

02:32PM is not a good idea because the results are variable and unpredictable.

Q. In your opinion, does the specification, the patent specification, inform a person of ordinary skill in the art that the inventors were in possession of a method for treating

02:32PM hormone dependent breast cancer in men?

A. No.

Q. Why not?

A. So, male breast cancer arises in a totally different environment. While it is a cancer in the breast as a

02:32PM location, the male's predominate hormone is estrogen -- is androgen, the ogesterone, and these tumors have arise in a testosterone resistant manner. While they are ER/PR positive, they also express androgens. Just because there are no trials in men, you can't automatically presume that everything that

02:33PM has been proven for postmenopausal women would automatically

apply to men. These are different characteristics, they have different prognoses, different sensitivity, even the hormones, even the estrogen receptors in the male breast are taught not to be functional. They express proteins in a different way. The presence of estrogen receptor makes them a different kind of a hormonal model and I would say that there is nothing to suggest that male breast cancer has similar treatment outcomes as female breast cancers.

Q. And does the patent provide any guidance on using fulvestrant to treat breast cancer in men?

A. No, it doesn't.

Q. And does the prior art say anything about using fulvestrant to treat hormone-dependent breast cancer in men?

A. No.

Q. Dr. Mehta, before we move on, if we could go back to demonstrative 48. So, I just wanted to ask you again, I think you had already explained about the teachings of Dukes with respect to premenopausal women, were there any other teachings that you are aware of in the art with respect to the use of fulvestrant in premenopausal women?

A. So, one of the important voices of that time was Mitch Dowsett and he says in 1995 that all the same -- it will be of value to determined the effect of fulvestrant on ER/PR of premenopausal breast cancer. And if you go on to Dr. Robinson's opinion in 2007, he goes on to say that fulvestrant

250 mg has no effect, zero, on hormone sensitivity and proliferation in premenopausal women with primary breast cancer measured at 14 to 21 days. So, the prevailing wisdom from the mid nineties and beyond, and even today, is that it's a different animal requiring different kinds of treatment programs.

Q. In support of your opinion, are you relying on Dowsett DTX-433 and Robinson DTX-881?

A. Yes, I am.

Q. Are you also relying on the DTX-309 Potter reference, the DTX-320 Clark reference and the DTX-311 Wittliff reference?

A. Yes, I am.

MS. PETERSON: Your Honor, we would move to enter those exhibits into evidence.

MS. PENSABENE: No objection, your Honor.

THE COURT: Okay. In evidence.

(DEFENDANT EXHIBITS DTX-433, 881, 309, 320 AND 311 WERE RECEIVED IN EVIDENCE)

BY MS. PETERSON:

Q. If we could move forward to DTX-49. Dr. Mehta, can you confirm you were relying on DTX-317 and DTX-318 in support of your opinions concerning treatment of breast cancer in men?

A. Yes, I was.

MS. PETERSON: Defendants move into evidence DTX-317 and DTX-318.

MS. PENSABENE: No objection.

THE COURT: In evidence.

(DEFENDANT EXHIBITS DTX-317 AND DTX-318 WERE RECEIVED IN EVIDENCE)

02:38PM BY MS. PETERSON:

Q. Now, Dr. Mehta, you also provided opinions in this case responding to Dr. Robinson's testimony concerning certain secondary considerations. Do you recall that?

A. Yes.

02:38PM Q. And one of those secondary considerations that Dr. Robinson has relied on is that Faslodex® has received acclaim and praise from the industry based on certain industry articles. Do you agree with Dr. Robinson's opinion?

A. I don't.

02:39PM Q. Why not?

A. Around the launch of products, as well as when there is a label change and the company needs to bring it again to the attention the oncologists, a lot of pharma newsletters, announcement at meetings, press releases start to talk about

02:39PM the drug. Also review articles start to appear. I see that more as part of marketing than actually sort of industry praise. And a lot of things that are appearing in pharma newsletters about the new product or a new indication are put there to basically bring it to the attention of the treating

02:39PM community that such a change is happening and in case they

have missed it.
Q. So, in your opinion are reports from practitioners better indicators of industry recognition?
A. They are.
02:39PM Q. Now, earlier we talked a lot about Dr. Howell and his clinical study in the nineteen nineties. Right?
A. Yes.
Q. Has Dr. Howell commented on the performance of fulvestrant compared to other hormonal therapies since it was
02:40PM launched in the two thousands?
A. Howell's opinion was compared with other hormonal therapies, the performance of Faslodex® was equivalent, nothing better.
Q. Now, Dr. Robinson also testified that Faslodex® has
02:40PM received acclaim and praise from those in the industry based on the inclusion of Faslodex® in clinical guidelines. Do you agree with that?
A. No, I don't.
Q. Why do you not agree with that?
02:40PM A. So, let's take the most formidable American guidelines of NCCN. NCCN is staffed by oncologists from all major NCI designated cancer centers, and these are the leading experts in their area of interest, and they look at all the evidence and add new indications or new drugs as they see fit. But
02:41PM they are obligated to add an agent to the list of agents

approved for that indication if FDA gives an approval. Because FDA approval is one of the stamps saying okay, for this particular paradigm you can use this particular drug.

So, it's almost automatic that guidelines will adopt a drug into their algorithm of treatment when it receives FDA approval, because when a physician opens up those guidelines, he needs to know the drugs listed there have been approved by FDA for the disease.

Q. Are you aware of any instances where a guideline has failed to recommend Faslodex®?

A. There is a British guideline which is very well respected in the industry which ruled otherwise.

Q. And which guideline was that?

A. The NICE one. I think it's the next one. That's correct.

Q. And what is NICE?

A. So, this is the National Institute of Health and Care Excellence, it's based in the UK. And drugs, as they enter the treatment formulation in the National Health Service and otherwise, the NICE takes a position on whether a new drug with all its claims of improvement, etcetera, is something they recommend for their patients. And as late as 2011 NICE basically said that fulvestrant is not recommended within its licensed indication as an alternative to aromatase inhibitors for treatment of estrogen in a separate positive, locally

advanced or metastatic diseases in postmenopausal women.
Q. One other opinion that Dr. Robinson offered was that Faslodex® has received acclaim and praise from the industry based on its use as a control arm of a clinical trial. Do you
02:43PM agree with that opinion?
A. No, I don't.
Q. Why not?
A. So, I think one has to understand why a drug gets into the control arm. A drug company wants to bring in a new
02:43PM product and they basically are looking at saying okay, this is a product and we're going to compare it against something else. And they would choose a drug -- sometimes if they can help it they will choose a drug where the company that is marketing the competitor arm, a drug that is used as control,
02:44PM joins into the research, joins into the expenditure, because these are very expensive trials. And the fact that Faslodex® was used as a control arm is largely recognition of the fact that AstraZeneca was pretty forward in making sure that it used their control arm in this trial. And that's a -- my take
02:44PM on that is that that basically is largely because these then become trials where the drugs are supplied free to the patients, and these are expensive drugs, still under patent, and the drug companies try to find partners where the competitor drug is supplied.
02:44PM Q. Is your testimony based on DTX-10-53?

A. The NCCN, yes.
Q. I'm sorry. Did we have the wrong slide up? Okay, go back. So the DTX-10-53.
A. 10-53.
02:45PM Q. And if we could go back to DTX-10-52. Your testimony about whether Faslodex® was included in the NICE guideline, was that reference to DTX-10-52?
A. Yes.
Q. And the opinions that you've just offered with respect to
02:45PM whether Faslodex® has received industry praise, were your opinions from a perspective of a person of skill in the art prior to 2000?
A. Yes.
Q. Just so I didn't -- I don't want to make anything
02:46PM confusing, I wasn't meaning just your opinions relating to secondary considerations were from the perspective of one of skill in the art of 2000, and that applies to all of your opinions, correct?
A. Yes.
02:46PM Q. Now, Dr. Robinson has also offered opinions regarding unexpected results as well, right?
A. Yes.
Q. Do you agree with Dr. Robinson's opinion that Faslodex® has unexpectedly improved side effects profiles?
02:47PM A. No.

Q. Why not?
A. So, if you are looking at the prior art before January 2000, the prevailing works, the major research are summarized on this slide. Howell is again saying that the
02:47PM long-acting administration of 4 mL was tolerated locally without any problems.
THE COURT: Was tolerated locally?
THE WITNESS: Without any problems.
A. Howell again said that the greater exposure was not
02:47PM associated with any increased side effects or efficacy. Howell again stated that the product was associated with high response rate and long experienced duration in patients previously treated with tamoxifen. But even down to -- and then I quote Wakeling, who basically went on to say that
02:47PM analysis of bone density in rats on Faslodex® did not reveal any deleterious effects.
So, all of the prior art we have looked at that comes to Howell and beyond, one of the remarkable things everybody notes is that its side effect profile is very good and that
02:48PM then should not come as a surprise now.
Q. And, for the record, is your testimony in relation to DTX-10-054?
A. Yes.
Q. And is it based on JTX-11 and DTX-49?
02:48PM A. Yes.

Q. Dr. Mehta, just going back to a topic one more time that we covered before. Would there have been a motivation to use a long-acting castor oil-based formulation of fulvestrant to treat hormone dependent breast cancer before 2000?

02:49PM A. Yes.

Q. And can you explain why?

A. So, the linear progression of preclinical to clinical studies which showed that there was efficacy, there was safety, there was a method of delivery. The method of

02:49PM delivery was a once a month type of injectability possible. The Phase I studies showing safety and efficacy in terms of estrogen receptors, Phase II showing efficacy and again safety, all the 19 women had hardly any side effects, all these things lead you to the point where you say okay, the

02:49PM drug has promise and a person of skill in ordinary art would basically consider it as something that would be interesting enough to explore further.

Q. And likewise, would there have been motivation to use a long-acting castor oil-based formulation of fulvestrant to

02:50PM treat hormone-dependent breast cancer before 2000 as administered intramuscular by 5 mL injections?

A. Yes.

Q. And why is that?

A. So, again, Howell uses that formulation and brings his

02:50PM results. And that's a formulation that is --

THE COURT: He uses that formulation and brings his what?

THE WITNESS: Brings his efficacy that we have described. And he basically brings up the possibility of having a therapeutic agent that can be administered monthly by intramuscular depot progressions and reducing the need for more frequent injections.

02:50PM

MS. PETERSON: Defendants also move to enter the following exhibits into evidence: JTX-1, JTX-3, JTX-4, PTX-432, DTX-282, DTX-287, DTX-306 and DTX-307.

02:51PM

THE COURT: Any objection?

MS. PENSABENE: Let me just ask, are these the exhibits that were discussed here?

MS. PETERSON: They were discussed in the last section on secondary considerations plus the patents.

02:51PM

MS. PENSABENE: No objection, your Honor.

THE COURT: Okay, in evidence.

(DEFENDANT EXHIBITS JTX-1, JTX-3, JTX-4, PTX-432, DTX-282, DTX-287, DTX-306 and DTX-307 WERE RECEIVED IN EVIDENCE)

02:51PM

MS. PETERSON: Pass the witness.

THE COURT: Okay. So this is a good time to take our break. So I was in the middle of a sentencing. I don't think it will go maybe 20 minutes. So if I can ask you to just -- we'll take about a 20-minute break, okay? You can sort of pop in and see in we're done. So, don't get too comfortable.

02:52PM

Okay. We'll pick right back up. All right?

THE DEPUTY CLERK: All rise.

(Brief Recess at 2:52 p.m.)

THE COURT: Whenever you're all ready. Sorry for the delay.

Ms. Peterson, can I give you back the reply report?

MS. PENSABENE: Thank you, your Honor.

THE COURT: As I indicated, counsel, we'll go to about 5:00.

MS. PENSABENE: Thank you, your Honor.

THE COURT: Okay?

MS. PENSABENE: Thank you, your Honor.

(CROSS-EXAMINATION OF DR. MEHTA BY MS. PENSABENE:)

Q. Good afternoon, Dr. Mehta.

A. Good afternoon, counselor.

Q. It's nice to see you again.

A. Same here.

Q. Dr. Mehta, you said that McLeskey had a very unique idea, right? You remember that?

A. Yes.

Q. And you said she had success from the viewpoint she was trying to prove. And that's hormonal independence, right?

A. That's correct.

Q. Now, you used the term "powerful antiestrogen agent" several times during the discussion of McLeskey. She never

used those words, right?
A. No, subsequent and proceeding prior art had used terminology saying the most advanced. And the evidence also had suggested that this was powerful enough to be used in
03:41PM tamoxifen resistant breast cancer patients, it was a powerful new agent.
Q. That's your interpretation?
A. Yes, it is.
Q. That's not the interpretation of Dr. McLeskey's paper, is
03:41PM that right?
A. No.
Q. Now, you talked about Dr. McLeskey's paper using a particular formulation. So to be clear, there were two formulations of fulvestrant in that paper, isn't that right,
03:41PM and she used both of them?
A. Yes, she did.
Q. And she doesn't distinguish between them, does she?
A. No.
Q. And so your point is -- I want to make sure I'm getting
03:42PM this right.
Your point is that she selected the compound for study not the formulation, right?
A. I think she selected the formulation.
Q. You agree that she used two formulations interchangeably,
03:42PM don't you?

A. She has mentioned both formulations, yes.
Q. And you agree she used then interchangeably, right?
A. I'm not sure what you mean by "interchangeably."
Q. She doesn't distinguish between one from another?
03:42PM A. She used both phrases, yes.
Q. And you'd agree with me there's nothing in the paper -- no data in the paper that compares the two formulations, no data in the paper that says that one -- or statement in the paper that says one formulation is better than the other
03:43PM that's right?
A. That is correct.
Q. And you would also agree with me that all of the formulations in that McLeskey paper are animal formulations, right? You'd agree with me on that?
03:43PM A. Yes.
MS. PENSABENE: Okay. And let's put --
BY MS. PENSABENE:
Q. So you'd agree with me --
MS. PENSABENE: Let's put up that McLeskey methods
03:43PM section.
Thank you, Mr. Hoy.
BY MS. PENSABENE:
Q. So you'd agree with me that McLeskey's is four different antiestrogen compounds. And for the letrozole formulation,
03:43PM that's not a commercial formulation, right?

A. No.
Q. That's a research formulation for use in animals, right?
A. That's correct.
Q. And for her experiments with tamoxifen, McLeskey used a preformulated pellet that's only sold for animal research and that's not the formulation for humans either, right?
A. That's correct.
Q. Okay. That's an animal formulation, right?
A. Yes.
Q. Okay. And you would agree with me that the peanut oil formulation that McLeskey uses similarly is the animal research formulation that's used in the early preclinical research that you discussed during your direct testimony, right?
A. Yes.
Q. And I think you already agreed with me, let me just be sure, McLeskey is about hormone independent pathway?
A. That is correct.
MS. PENSABENE: You know what, I just want to keep track of stuff, so do you mind if I write some things down on the board?
Your Honor, may I approach and use that chart?
THE COURT: You may.
BY MS. PENSABENE:
Q. I hope you will indulge my handwriting. I apologize.

It's -- I'll try to be neat.

So I've written here McLeskey and under it hormone independent. You'd agree with that?

A. Yes, I would.

03:45PM Q. Okay. Now, if you could take a look, please, at the method section for the formulations that were used of fulvestrant, you would agree with me that both of those formulations were administered subcutaneously, is that correct?

03:45PM A. That is correct.

Q. Okay. I'm just going to write that down here on this chart then.

And you'd also agree with me, right, Dr. Mehta, that the fulvestrant formulations, the two fulvestrant formulations

03:45PM were both administered once weekly?

A. That is correct.

Q. So if I write "weekly" on the chart, that expresses what we just agreed upon?

A. Agreed.

03:46PM Q. You would also agree with me that in the McLeskey system, the fulvestrant formulations were cross-resistant with tamoxifen, is that right?

A. Say that again?

Q. In the McLeskey system --

03:46PM MS. PENSABENE: We can pull up the title, perhaps,

Mr. Hoy?

THE WITNESS: That's okay. Go ahead.

Can you repeat the question?

BY MS. PENSABENE:

03:46PM Q. In the McLeskey system the fulvestrant formulations were cross-resistant with tamoxifen, is that right?

I'll just read the title for you, Dr. Mehta, and maybe that will help.

THE COURT: Were the formulations that she used

03:46PM cross-resistant with tamoxifen?

THE WITNESS: I think basically says the cell line is cross-resistant. Where does it say it is cross-resistant to tamoxifen?

BY MS. PENSABENE:

03:47PM Q. Let's read the title together. Okay?

A. So I read for you.

Tamoxifen resistant FGF-transfected MCF-7 cells are cross-resistant *in vivo* to the -- Faslodex is the other approach. So that means they don't respond to these products

03:47PM not tamoxifen. It's a fancy way of saying this is a hormone independent cell line, that's how I interpret this particular title.

Q. Okay. So you don't interpret this title to mean that the cells are resistant to both ICI 182,780 and tamoxifen?

03:48PM A. Basically she's talking about cell lines being

cross-resistant in terms of these three products she used, which is another way of saying these are independent of these three hormonal manipulator drugs.

Q. So I can write here on my chart cross-resistant? I just want to be accurate in what your opinion is.

A. Yes.

Q. Okay. I'll go back over here so I'm not leaning over your shoulder, Dr. Mehta. Sorry about that.

Okay. Now, you would agree with me that the McLeskey paper doesn't give any data on the extent of estrogen pathway suppression for any of the compounds that were used in any of the formulations, correct?

A. Correct. Yes.

Q. And you would agree with me, too, that the McLeskey paper doesn't gave any pharmacokinetic data for any of the treatments that were used, right?

A. That is correct.

Q. Also the McLeskey paper doesn't give any data on antiestrogen effect for any compound used, right?

A. Yes.

Q. Now, the only results that are given for the formulations with ICI 182,780 for fulvestrant is that it is a treatment failure, right?

A. No.

Q. Do you disagree with me that McLeskey describes the

results with ICI 182,780 as a treatment failure?
A. Basically it's one way of saying that these are independent cells that are not possible to be manipulated by three powerful antiestrogens. And if that's what you mean by the question, I agree.
Q. And those are the words that were used by Dr. McLeskey in her paper is "treatment failure," you'd agree with that, right?
A. Yes.
Q. And you'd also agree that Dr. McLeskey in her paper says that treatment with fulvestrant does not inhibit tumor growth, right?
A. That is correct.
Q. And you'd also agree that Dr. McLeskey says in her paper these treatments did not slow estrogen independent growth or prevent metastasis of tumors, right?
A. That is correct.
Q. And your goal in treating a patient with hormonal dependent breast cancer is indeed to slow growth and prevent metastasis, is that right?
A. By and large, yes.
Q. And I think you used the term "successful." But McLeskey doesn't use the word "successful" about the use of any of the fulvestrant formulations within her paper, does she?
A. What it basically means is she was testing that these are

hormone independent cell lines, which normally are hormone sensitive because of MCF-7, and she has created a cell line which are totally independent than using these drugs and showing that they are hormone independent is a successful experiment because that's what she was trying to show. So success is basically proving the hypothesis.

Q. And you agree there's no data about an estrogenic effect of these compounds, right?

We'll move on. I'll withdraw.

Okay. I think you cited a connection with the Howell paper from McLeskey, right?

A. Yes.

Q. Okay. And you included a footnote that cites to Howell but you didn't include what that citation was for. So can we look together as to what that citation was for?

A. Yes.

Q. What I did, I took your slide and put that together, and you should check it and make sure it's right.

MS. PENSABENE: Can you pop that up, Mr. Hoy? I think it's -- we put it together with Dr. Mehta's slide.

BY MS. PENSABENE:

Q. Just so we're on the same page. Okay?

A. Right.

Q. Here we go. Sorry about that.

Okay. So you had cited to Footnote 19, and that's a

Howell paper. So let's look first at what McLeskey says in the abstract. She says that only 30 to 40 percent of patients have a positive response to second hormonal therapies, and then she calls that a lack of response. Do you see that?

03:53PM A. Yes.

Q. Okay. And then she goes on to explain within the body of the paper, and there she says that, early results for small numbers of tamoxifen resistant patients have shown that only about 30 to 40 percent of such patients have a positive

03:53PM response to subsequent ICI 182,780 or aromatase inhibitor therapy. Do you see that?

A. Yes.

Q. And that's where she cites Howell, isn't that right?

A. Yes.

03:54PM Q. She cites it as one of a series of papers about endocrine therapy, right?

A. Right.

Q. And her point being endocrine therapy doesn't work all that well so we're looking for another pathway to work on,

03:54PM isn't that what she's saying?

A. Yes.

Q. She's distinguishing what she's doing from endocrine therapy, right?

A. Right.

03:54PM Q. Okay. And I think that's been some of your point, right,

Dr. Mehta?
A. Yes.
Q. That this is different, totally different from endocrine therapy.
03:54PM A. That's correct.
Q. I'm sorry, let me make sure I'm clear.
This is totally different from hormonal dependent pathways, right?
A. That is correct.
03:54PM Q. Okay. All right. And now in thinking about the McLeskey paper and sort of where it fits into this time line, you had noted several times I think today the names of some well-known researchers, and you noted Dr. Robertson and Dr. Howell, and some people also from AstraZeneca.
03:55PM A. Yes.
Q. Dr. Wakeling and Dr. Dukes. So let's take a look at the McLeskey paper.
MS. PENSABENE: Can you pull up the front of the paper, please, Mr. Hoy? And that's JTX-10. Great. There we
03:55PM go.
BY MS. PENSABENE:
Q. Okay. You would agree with me, right, Dr. Mehta that none of these folks that are authors on this paper or any of those researchers that you've been naming and none of them are
03:55PM from AstraZeneca, right?

A. That is true. This is the Lombardi Cancer Center, which was independent of the research going on in the UK.
Q. Okay. And you would agree with me, right, that there were other researchers who had used fulvestrant as a research
03:56PM tool in their work with animals, right?
A. Yes.
Q. Okay. So you would agree with me, like, for example, the Al-Matsubi reference, I think you and I talked about that at your deposition.
03:56PM A. Yes.
Q. You would agree with me that that reference was looking at the estrogenic cycle in sheep also used fulvestrant and that used it for basic animal research and injected it intramuscularly, right?
03:56PM A. I would have a look at it.
Q. I can show that to you and see if you agree.
A. Please.
Q. I want to make sure we're right on the same page.
MS. PENSABENE: May I approach, your Honor?
03:57PM THE COURT: Yes.
MS. PENSABENE: May I hand you one?
THE COURT: Yes. Thank you.
BY MS. PENSABENE:
Q. And, Dr. Mehta, this work is just also basic animal --
03:57PM Let me just clarify. This is PTX-693. So the record

will be clear, it's the Al-Matsubi paper.
BY MS. PENSABENE:
Q. And this is just talking about the compound fulvestrant, its using it in animal research. This time it's injecting the
03:57PM compound intramuscularly into sheep and it's the same kind of situation, some basic animal research, right?
A. Yes.
Q. Okay. And here also they, to the last page, the researchers thanked ICI Pharmaceuticals for their gift of the
03:58PM compound, right?
MS. PETERSON: Your Honor, we object to this line of testimony on the Al-Matsubi reference. Dr. Mehta did not provide any opinion about this on direct testimony and I think it's not in the scope of his expert reports as well.
03:58PM MS. PENSABENE: Actually, it's in the scope of his report.
That was the last question, anyway. The point being the compound was used for basic animal research and in a number of different --
03:58PM THE COURT: That's for the general proposition?
MS. PENSABENE: I'm sorry?
THE COURT: For the general proposition?
MS. PENSABENE: Yes, exactly, your Honor. No specifics about that.
03:58PM THE COURT: Okay. For that purpose I'll permit it.

BY MS. PENSABENE:

Q. Now, just to finish off talking a little bit about McLeskey here. I want to just get an idea where McLeskey falls on this picture we've got here to understand where it is in the pathways if you don't mind.

So you'd agree with me, Dr. Mehta, that McLeskey is looking at FGF, one of these growth factors, right?

A. Right.

Q. As a possible pathway for hormone independent breast cancer, is that correct?

A. Yes.

Q. Okay. So if I put this up here, that's correct that McLeskey is FGF hormone independent. And I've circled the FGF receptor in these growth factor pathways.

A. Yes.

Q. And that's different from the estrogen receptor and the hormonal dependent pathways, is that right?

A. That's correct.

Q. And I think that was your point, right?

A. Yes.

Q. Okay. Let's go back a little bit and talk about options for active ingredients for treatment for hormonal dependent breast cancer. Okay?

You would agree with me, right, that by 2000 treatment that had been used for hormonal dependent breast cancer

included tamoxifen, other SERMs, third generation aromatase inhibitors and other aromatase inhibitors, progestin, androgen, hydro estrogen. Do I have it right?

A. Yes.

04:00PM Q. Okay. And so the SERMs, those were a proven mechanism, right?

A. That's correct.

Q. And aromatase inhibitors also proven mechanism, right?

A. Yes.

04:01PM Q. And the progestin, also proven mechanism?

I think you have to answer audibly so we get it on the record.

A. Yes. Yes.

Q. Thank you.

04:01PM And the androgen, those are also a proven mechanism?

A. Yes.

Q. And the hydro estrogens, also a proven mechanism?

A. Old fashion but, yes.

Q. All right. And all those categories are still being

04:01PM investigated for improvements?

A. I would disagree. The hydro estrogens, the megestrol type of categories, the agents that target the progestins, they're becoming less of an interest because the direct drugs that were evolving for estrogen related pathways were far more

04:02PM interesting and powerful. So you're right, in general these

were the options available at that time.
Q. And in fact antiprogestins were being researched at this time as promising options, is that correct?
A. Yes.
04:02PM Q. And I think you'd agree lots of ideas about approaching the estrogen receptor positive breast cancer, right?
A. Correct.
Q. And probably every group considered their idea the best and touted it in their papers, right?
04:02PM A. I would suppose so, yes.
MS. PENSABENE: And, Neil, can you put up our chart, of some of these promising compounds, please?
BY MS. PENSABENE:
Q. And so you would agree with me that there was research
04:02PM and promising compounds being -- being researched in all of these categories, the aromatase inhibitors, the SERMs, the androgens, the antiprogestins, the pure antiestrogen, the progestins?
A. Yes.
04:03PM Q. And in your direct, you didn't talk about any of these specific compounds, right? Like, you didn't talk about Vorozole, for example, right?
A. No, I didn't.
Q. And you didn't compare what was known about any of these
04:03PM compounds --

A. No.
Q. -- to fulvestrant, right?
A. That's correct.
Q. Okay. Now, let's just look at those pure antiestrogens if we could for a second.
04:03PM
There were -- this was a small -- a small class, right?
A. That's correct.
Q. At the time in 2000, right? There's only -- there's only five of them and two of them are related, the EM compounds, right?
04:03PM
A. Yes.
Q. In your direct, you didn't address EM 800 which is a pure antiestrogen that had some promising Phase II results that had been published and were currently in Phase III, right?
04:04PM
A. No, I didn't, no.
Q. So you didn't consider that in your thoughts about fulvestrant. Now --
A. I would take exception to that statement. The issue here is that, yes, these products at that time were also being
04:04PM
worked on. But if you look at the team from ICI and subsequently AstraZeneca that had been currently developed tamoxifen, and then subsequently anastrozole, a very reputable group of doctors who were focused on, mid-1980s, '90s, or even earlier on one product, because national interest in meetings,
04:04PM
they pronounced as the most advanced antiestrogen and had a

clear track record in the research proceeding seamlessly from preclinical data of efficacy and toxicity to clinical efficacy and safety clinical data and corroborative presentations all the way up to Dr. Robertson in 1999 in San Antonio.

04:05PM So while these other products were certainly around, it is not unreasonable that based on that kind of testimony, I would pick fulvestrant as a drug development.

Q. You would agree with me, wouldn't you, Dr. Mehta, that Dr. Howell and Dr. Robertson and Dr. Dowsett all worked on

04:05PM aromatase inhibitors, on SERMs, on antiprogestins. You would agree with that, right?

A. I would agree with that, yes.

Q. Okay. So those groups have worked on all these different options?

04:05PM A. I have a clarification.

THE COURT: You had a clarification, but let her finish the question first and then you can clarify.

What was your question?

BY MS. PENSABENE:

04:06PM Q. Okay. So let me rephrase -- because now, I have totally forgotten my question, I'm sorry.

THE COURT: That's okay.

BY MS. PENSABENE:

Q. So you would agree with me, right, that you started with

04:06PM fulvestrant because that's what the patent is about, right,

Dr. Mehta?

A. No. I -- a hypothetical POSA would find this product of interest is what we're talking about here.

THE COURT: Okay. I think I might be confused now. What is it that you wanted to clarify earlier? I don't want the record to not be complete. What is it?

THE WITNESS: So while the team that was mentioned as the team working on other products, the same team basically was not only mentoring this product into clinical studies, but at every national forum and international forum was talking about it, so if one was -- there were already great products coming in, aromatase inhibitors, such as anastrozole, letrozole, exemestane, and that if somebody is interested in developing a new product with a new mechanism of action, there was no sense going there.

All the competitors of the SERMs, were again not proving to be either better than tamoxifen or safer than tamoxifen. And so one category that stood out to be novel, with a new mechanism of action, with lack of cross-resistance with tamoxifen, that was again by this team that had been heralding all these important drugs, had been touting it as the new major advance, that is probably the reason why it would be reasonable to expect that a POSA would find that product ahead of others and develop it.

BY MS. PENSABENE:

Q. Okay. So, Dr. Mehta, your opinion doesn't address the data or literature from any of those other compounds. It's looking at the -- you're just looking at the team that had worked on fulvestrant, right?

04:08PM A. Looking at the team and the massive amount of prior art that is accumulating basically in support of this particular product.

Q. Okay.

THE COURT: But it sounds -- I'm sorry.

04:08PM MS. PENSABENE: Oh, I'm sorry, Your Honor.

THE COURT: But it sounds like your opinion includes an assessment that given the prior success that the team at AstraZeneca had, that you would expect fulvestrant to be further developed. Does that sound --

04:08PM THE WITNESS: Absolutely.

THE COURT: That's what you're saying.

THE WITNESS: I am.

THE COURT: Okay.

BY MS. PENSABENE:

04:09PM Q. Dr. Mehta, you would agree with me, wouldn't you, that there is another AstraZeneca pure antiestrogen on this list, too, right?

A. Yes.

Q. Okay. And that one was ultimately not successful, right?

04:09PM A. That is correct.

Q. And you would agree with me that the Howell and Robertson and Dowsett team have worked on many of these compounds and, in fact, many of them were -- all -- in fact, all of then, except for fulvestrant, were unsuccessful, isn't that right?

04:09PM A. That is correct.

Q. Okay. Now during your direct today, you discussed the 1999 San Antonio Breast Cancer Symposium. Do you remember that?

A. Yes.

04:09PM Q. Okay. And you would agree that the '99 San Antonio abstract book contained over 440 abstracts, right?

A. Yes, that's correct.

Q. Now, you used a methodology to sort of narrow that down, and in that methodology, you excluded the growth factor

04:10PM treatments, right, because you considered them to be not relevant to the question here, right?

A. So I just considered the hormone-related treatments of breast cancer.

Q. And I think you said, and correct me if I'm wrong --

04:10PM THE COURT: Excuse me, treatments of breast cancer.

BY MS. PENSABENE:

Q. I think you said what was recommending the Robertson '99 abstract to you, was that it was the only one that was about a novel agent, is that right?

04:10PM A. By and large, yes.

Q. I'm sorry?
A. By and large, yes.
Q. Oh, okay. I just want to take a look at the page that the Robertson abstract is on.
04:10PM That's at -- it's not JTX-13.
MS. PENSABENE: And I'll ask Mr. Hoy, would you mind popping that up on the screen.
BY MS. PENSABENE:
Q. And this is in your book, too --
04:11PM A. Yes.
Q. -- Dr. Mehta, that's over there on the side from your direct. So what I'd like to do, this is -- this is the -- this is the abstract that you were talking about, about Dr. Robertson, but I'd like to look up on the same page, if I
04:11PM could, up at an abstract in the -- catty-corner to this. It's Abstract No. 25.
So you would agree with me, Dr. Mehta, that this is talking also about a hormone-dependent endocrine -- also about an endocrine therapy, right?
04:11PM A. Yes.
Q. It's about a SERM, right?
A. Yes.
Q. And this is also about a novel compound, right?
A. Yes, it is.
04:12PM Q. It's about a novel SERM. This one is about LY 353381.

A. Yes.
Q. That's correct, right?
Okay. So there were a lot of novel compounds -- there were other novel compounds. Let me be more accurate. There
04:12PM are other novel compounds, weren't there, other novel endocrine therapies that were being discussed in the general session at San Antonio, right?
A. So this particular paper was discussed in the general session? Can we confirm that?
04:12PM Q. Mm-hmm. Yes, yes, it's part of that --
A. Okay.
Q. It's part of those general session discussions.
A. So I stand corrected. There might have been more than one.
04:12PM Q. Okay. And then looking on this same page, this page also talks about Raloxifene and discusses Arimidex, right? And those are also endocrine therapies, right?
A. Arimidex has already been approved by that time and so it's not an oral therapy. It's already on its way to becoming
04:13PM a standard of care for postmenopausal women. Raloxifene, the data is basically moving it towards a treatment for osteoporosis and prevention of breast cancer. The data for treating breast cancer itself in hormone-dependent category for Raloxifene is five, three years at the most, it doesn't
04:13PM really stand out -- it's being moved towards treatment of

osteoporosis, because it improves the bone health, but in terms of comparing it to the anticancer properties of tamoxifen, it was proven to be not equivalent.

Q. Okay. Then you would agree with me, right here on the same page as the Robertson 1999 abstract, there are at -- there's an abstract for a novel SERM, another SERM, and a aromatase inhibitor, is that correct?

A. True.

Q. In the general session --

A. Yes.

Q. -- of San Antonio. And that's just a snapshot, right?

So -- and you would agree with me that EM 800, which was another pure antiestrogen was -- had reported high response rates in Phase II trials by 2000 and was currently in Phase III trials, right?

MS. PETERSON: Your Honor, I object to this line of questioning. I don't think this has anything to do with the abstract from the San Antonio Breast Cancer Conference. That's outside the scope of his direct testimony.

MS. PENSABENE: Your Honor, this goes directly to credibility, because this witness has testified -- is testifying that one would choose fulvestrant as the most advanced of all the anti -- pure antiestrogens, EM 800, as an antiestrogen. This was published before 2000.

It is phase -- it's in Phase III trials and it has

promising Phase II data. It directly goes to the -- to the witness's opinion about fulvestrant.

THE COURT: To his opinion that fulvestrant is the -- what --

04:15PM MS. PENSABENE: His opinion was that fulvestrant was the most advanced of all of -- if you could put the chart back up, just so I can -- I know there's a lot of names, sir, floating about.

THE COURT: Why would you quarrel with that?

04:15PM MS. PENSABENE: I'm sorry?

THE COURT: Why would you quarrel with that?

MS. PENSABENE: That fulvestrant was the most advanced at this time in 2000?

THE COURT: Yes.

04:15PM MS. PENSABENE: I would quarrel with it because I don't -- I disagree that fulvestrant was the most advanced and the clear choice here.

MS. PETERSON: And we would also disagree with her characterization of Dr. Mehta's testimony. I don't believe

04:15PM that he's offered an opinion that it was the most advanced. He was simply reporting what others in the literature reported and described it as including Dr. Robertson and other people.

I believe Dr. Mehta's testimony was limited to expressing reasons why people would be interested in pursuing

04:16PM tamox -- in pursuing fulvestrant, but not necessarily that it

was the most advanced.

THE COURT: So the dispute is the words "most advanced."

MS. PETERSON: Well, and also the line of questioning asking Dr. Mehta about other compounds that he did not discuss within his direct testimony.

THE COURT: Well, do you agree with what Ms. Pensabene said that at the time that fulvestrant was the most advanced of these pure antiestrogens?

04:16PM THE WITNESS: So if you're looking at --

THE COURT: Can you just answer that with a yes or no? And if you don't understand the question, then you have to tell me.

THE WITNESS: Yeah, please repeat the question.

04:16PM THE COURT: Yeah. Do you agree that at the time, in 2000 -- 2000, is that the question?

THE WITNESS: Right, 1999, 2000, yeah.

THE COURT: That fulvestrant was the most advanced?

THE WITNESS: That is correct. That was --

04:17PM THE COURT: In terms -- of the purest antiestrogens, you agree with that.

THE WITNESS: Yes.

THE COURT: So then if Ms. Pensabene wants to impeach that statement, she may, despite the fact that he did or did

04:17PM not -- well, I don't recall that he testified about EM 800,

but it's subject to impeachment, go ahead.

BY MS. PENSABENE:

Q. So Dr. Mehta, you would agree with me, right, that there had been promising Phase II data published on EM 800?

04:17PM A. Yes.

Q. And EM 800 was also by 2000 in Phase III clinical trials?

A. That is true.

THE COURT: It almost sounds as if you are saying, and correct me if I'm wrong, that Dr. Robertson shouldn't have

04:17PM been surprised by the results --

THE WITNESS: Yes.

THE COURT: -- that he achieved. So his testimony that he was, you --

THE WITNESS: I don't agree, yeah, right.

04:18PM THE COURT: You don't agree that he was surprised?

THE WITNESS: So I think, basically, in the preclinical phase and the clinical phase and before '99, there was already -- they, themselves, were saying that this was the most advanced product. They were mentoring it into clinical

04:18PM trials which happened right around this time, and it went on to receive approvals, an FDA approval.

So to subsequently say that this was not a -- you know, there was no surprise about it or people were surprised the drug was doing very well, is exactly contrary to what they

04:18PM presented at San Antonio, that this is the most advanced and

they want -- the further studies will continue. So I think there's a dichotomy there.

The same group that was developing this compound was very positive at that time and they would not have been shepherding it into further trials and presenting it to international audiences such as San Antonio, if they didn't believe that it was a compound with major potential and interest for them, and that's all I'm saying is that in looking at those options in that frame of time, if I'm looking for antiestrogen as one of the agents I want to use, it is reasonable that I would put this product for development.

THE COURT: Okay.

BY MS. PENSABENE:

Q. Dr. Mehta, you would agree with me, right, that there were prominent researchers who were looking at Vorozole for example, and touting its promise, is that correct?

A. Yes.

Q. And there were prominent researchers who -- at -- in 2000, were looking at ORG 33201 and touting its promise, right?

A. I have not seen any touting of promise by any of those, so I really have to generically agree, saying yes, everybody must be proud of what drugs they were working on. But as Dr. Robertson also indicated, some of these drugs were killed because they didn't seem to work. And so just because you

were working on it, doesn't mean they were touting it.

Here was a team very consistently saying they're a new product with promise, and they were calling it most advanced and advancing it in their clinical trials and using it on their patients in clinical trials. So I think that's basically the direction in which my mind would go when I'm looking at a possible product for development.

Q. Okay. Let me just see if I'm understanding you.

So your point is that because of this -- because this team was behind this product, it really didn't matter what the other choices were, or what the data on the other possibilities is, that you would pick whatever compound they were working on and saying was promising?

A. Again, that is a mischaracterization of what I'm trying to say.

THE COURT: Let me -- let me see if I understand what your testimony is.

Were you here when Dr. Robertson testified about the RU compound?

THE WITNESS: Yes.

THE COURT: Which, at the time was -- appeared to be promising. Do you agree with that?

THE WITNESS: Yes.

THE COURT: So are you saying that at the time that the ICI 182 appeared to be promising, the RU 58668 compound

appeared to be promising, but you have Team A and Team B and Team A sort of -- they hold the gold --

THE WITNESS: Mm-hmm.

THE COURT: -- medal?

04:21PM THE WITNESS: Yes.

THE COURT: And the RU team sort of holds the bronze medal. So are you saying, then, that all bets were on the ICI team? Is that what you're saying?

THE WITNESS: Something similar to that, but I would

04:21PM basically say it's not all based on one product. It's simply that you can look at the clinical evidence, the clinical evidence. The mounting body of evidence that suggest there's going to be a successful product and you look at the people who are developing it, their track record.

04:22PM THE COURT: The gold -- the gold medalist.

THE WITNESS: Right. So you basically both give the weight to the product and say, okay, this is the team, this is the body of data, why would I not go develop it.

BY MS. PENSABENE:

04:22PM Q. Dr. Mehta, you included in that team Michael Dukes, is that right?

A. He was one of the presenters, yes.

Q. And you looked at -- when you were talking about preclinical research, the two Dukes' papers?

04:22PM A. Right.

Q. Right? And you would agree, I think from what you're saying that Michael Dukes is a well-respected researcher in this field?
A. Yes.
04:22PM Q. Okay. And you would agree that Dukes has a very respectable track of work that led to the paper that you quoted?
A. Yes.
Q. Now, the Dukes works that you were -- the Dukes work that
04:23PM you were talking about earlier today was a valuation of fulvestrant in primates, right?
A. Yes.
Q. There were two papers, right?
A. Yes.
04:23PM Q. Now, in your timeline here, you don't include the Dukes '814 patent, do you?
A. No, I don't.
MS. PENSABENE: May I approach, Your Honor?
THE COURT: Yes.
04:24PM BY MS. PENSABENE:
Q. Now, the inventor of this patent, this is the Dukes '814 patent, right? It's JTX-18 for the record.
This patent is assigned to AstraZeneca, is that correct?
04:24PM A. Yes.

Q. And the inventor is the same Michael Dukes who we had been talking about and you had been looking at his work during your direct testimony, right?
A. That is correct.
04:24PM Q. Okay.
MS. PENSABENE: And can you pull up Example 3 of this patent, please?
BY MS. PENSABENE:
Q. And you would agree with me that this patent to Dr. Dukes
04:24PM is -- includes examples of formulations of fulvestrant, right?
A. Yes.
Q. And here, in Example 3, the patent describes a castor oil-based intramuscular injection that is 50-milligrams per milliliter and it has -- the composition is given, right?
04:25PM It's 40 percent benzyl alcohol, right?
A. Right.
Q. Okay. Now, that's not the same composition as in the formulation you were talking about earlier in the McLeskey --
A. It's not.
04:25PM Q. -- paper.
And the Dukes patent --
MS. PENSABENE: If we can go down a little further to the table.
BY MS. PENSABENE:
04:25PM Q. This patent -- the patent includes some data, too, on

antiestrogen activity, right?
A. Yes.
Q. So if we look at our timeline of AstraZeneca work and we can actually look at our timeline, that's back -- that's back behind us. You could see that Dukes patent is on there, right?
04:26PM
A. Yes, it is.
Q. Okay. Because that's part of the AstraZeneca work that was on fulvestrant, right?
04:26PM
A. That is correct.
Q. Okay. But you didn't consider the dukes patent, right?
MS. PETERSON: Your Honor, we object to this line of questioning as well, and Dr. Mehta did not opine on the '814 patent or offer any opinions during his direct testimony.
04:26PM
MS. PENSABENE: And, Your Honor, that's the point.
THE COURT: No, but it goes to the weight of his opinions.
THE WITNESS: So is this a yes or no answer, or is there any chance or elaborating what I mean by yes or no?
04:26PM
THE COURT: What you mean by what --
THE WITNESS: I mean, almost all of the questions are yes or no, but I do need to -- and I would love to agree with everything, you know, but I can't.
THE COURT: So in cross-examination, that is quite
04:27PM
typical.

THE WITNESS: I know that.

THE COURT: So Ms. Peterson will get up on redirect, if there's anything you need to explain, she will ask if there's --

04:27PM THE WITNESS: I get that, all right.

THE COURT: Okay. However, if a truthful answer to the question can't be answered with yes or no, then you have to tell Ms. Pensabene that you can't answer it with a yes or no. Okay?

04:27PM THE WITNESS: So I can't answer it with yes or no, the last question.

THE COURT: What, that you didn't consider the Dukes '814 patent?

THE WITNESS: No, that -- the answer to that is yes, 04:27PM but I can't do the last part. All right. Proceed.

BY MS. PENSABENE:

Q. Okay. And you -- in forming your opinions, you didn't consider whether the Howell paper that you talked about might have used the Dukes patent formulation, right?

04:28PM A. Look at the timeline. If Howell is being published in '95, '96, and McLeskey around that time is being supplied by AstraZeneca, Mr. Vose, with a castor oil-based intramuscular preparation or injectable preparation, why would AstraZeneca that is trying to test this product in clinical lines, as well 04:28PM as other investigators who requested, why would they supply a

product that was available from '80s and obviously was undergoing further development, because what McLeskey got supplied was a different formula.

So I basically would think that in terms of the timeline, what Howell got in his reserve were attributable to, must be the same product or similar one supplied by AstraZeneca in that timeline, because they were testing that product. Why would they pull out the product from the prior decade?

Q. You have no idea, right, you whether -- what formulations Howell used, right?

A. I don't have that idea, no. I'm just making logical conclusions.

Q. Okay.

THE COURT: Excuse me. Are you speculating?

THE WITNESS: I am. There is nothing in the literature to confirm my speculation.

BY MS. PENSABENE:

Q. If we could stay with your preclinical work. Looking at your slide DTX- 019, you would agree with me -- this is the Wakeling '91 paper. You would agree with me, wouldn't you, that what Wakeling is saying here is he wants to use fulvestrant to explore the possibilities of this unproven mechanism, right?

A. That is correct.

Q. Okay. Because it's an unproven mechanism. You don't even know how it's going to work, what's going to be the mechanism of action. So there is a lot of research to be done, right?

04:30PM A. That is correct.

Q. Let's take a look at your slide DTX-1-030. That's also in your preclinical work.

A. Yes.

Q. This is Wakeling 93. And I think here with this slide

04:31PM you did a dose conversion, right, from monkeys to humans from this paper. Do you remember that during your direct?

A. Yes.

Q. And your dose conversion from this paper was that the monkey dose used in discussing Wakeling 1993 was equivalent to

04:31PM a 250 mg dose for a woman, right?

A. Yes.

Q. And your opinion was that that dose, that 250 mg dose sustained 100 percent estrogen receptor blockade, right?

A. I was quoting the article, yes.

04:32PM Q. So, there is nowhere to go. You can't go up from there, right?

A. No.

Q. Now, let's turn our attention to the early clinical work, okay, in your timeline. All right?

04:32PM A. Yes.

Q. And let's talk about DeFriend. That's at JTX-15. Maybe we can pull up your Slide 38. Now, I just want to make sure we're on the same page here because I see that you have some highlighting in the authors and highlighting in the institutions that they are with. Dr. DeFriend and Dr. Howell and Dr. Robinson, they are not with Zeneca, right?

A. No.

Q. So you are just highlighting Zeneca to --

A. There is a separate highlight in the names that are recognized and seem consistent through research papers, I highlighted simply to point out the commonality.

Q. In your view someone of skill in the art could not start with the DeFriend formulation as being one that had been used with success, right?

A. That is correct.

Q. And one wouldn't take from the DeFriend study a teaching of once-daily dose, right?

A. DeFriend was basically looking for side effects. It's -- but one would not take that dose as a dose one wants to double up in a once a month depot injection, it's that's just the data, that's how they used it over their 7-day period.

Q. So, DeFriend is -- in your view DeFriend is looking at side effects not at --

A. And efficacy.

Q. Okay. But not on the issue of daily dose, right?

A. That's what he uses so that's the -- that's one of the features of that particular trial, is that 7 days before surgery they give them a -- non daily doses.

Q. Dr. Mehta, you are familiar with the experience with endocrine therapies that greater doses even without toxicity did not lead to increased efficacy, right?

A. I'm familiar with that.

Q. And, for example, anastrozole was tolerated at 10 mg and 1 mg, but there is no additional clinical benefit for the higher dose, right?

A. That is correct.

Q. And that was known in 2000?

MS. PETERSON: This is outside the scope of his testimony as well.

THE COURT: Sustained.

MS. PENSABENE: Your Honor, he testified about dosing and he testified and he did multiplication from DeFriend and said you could come to a different -- and he talked about maximum tolerated dose. This is directly relevant to that testimony.

THE COURT: But I don't think he talked about efficacy.

MS. PENSABENE: That's exactly what he was talking about, your Honor. He was talking about maximum tolerated dose, that there would be a reason to increase dose. And he

said you would go to a maximum tolerated dose, that would be the theory that would apply. Not so. And now testing that theory because the endocrine agents do not fit in that theory, that is not how dosing is done -- was done with the endocrine agent at this time.

04:35PM

MS. PETERSON: We would disagree. Dr. Mehta was not drawing an opinion based on -- drawing an opinion of efficacy based on the dosing.

THE COURT: Did you render an opinion about the dosage and the correlation between dosing and efficacy?

04:36PM

THE WITNESS: No, ma'am.

THE COURT: What were you talking about when you talked about the maximum dose?

THE WITNESS: It sort of points out that if you look at this dose, it gives you some idea of how -- if you were to take this on a daily basis for 28 days, how it might actually calculate to a different dose level than 250. So, it's possible that that dose could enter the calculations in future. But beyond that, you can't make any other assumptions.

04:36PM

04:36PM

THE COURT: Yes. I don't think he was correlating it with efficacy.

THE WITNESS: Not at all.

THE COURT: I think he was saying that -- looking at DeFriend was during a short period of time, but if you did the

04:36PM

math or some -- I don't remember --

THE WITNESS: So it's 28 times 18.

THE COURT: Did the math, you would come out at approximately 250 monthly. I thought that's what he was discussing.

04:37PM

MS. PENSABENE: That you would come out with 250?

THE WITNESS: 500.

THE COURT: 500.

MS. PENSABENE: And as long as Dr. Mehta is not talking about efficacy related to that dose or is not talking about a reason to go to an increased dose from 250, if that's -- as long as he's not testifying about that, then we'll move on. But our point being we should have the opportunity to question that opinion if he is testifying that that was a reason to go to a higher dose.

04:37PM

04:37PM

THE COURT: I understood, correct me if I'm wrong, the import of your testimony was with respect to that publication that you can't necessarily discount the value of that publication because of the lower doses because that was a 7-day dosage.

04:38PM

THE WITNESS: Right.

THE COURT: But if you did the math you would come close on a monthly basis to 500.

THE WITNESS: Yes.

THE COURT: And you did that simply -- did you do it

04:38PM

because you correlated it to efficacy?

THE WITNESS: Not at all.

THE COURT: Okay. Does that resolve the issue?

MS. PENSABENE: As long as DeFriend is not going to be used as an argument for going to a higher dose.

04:38PM

THE COURT: Well --

MS. PETERSON: Well, I think that -- you know, if DeFriend, if the data can be extrapolated to convert it to a once monthly dose of 500 mg, that's what it is.

04:38PM

MS. PENSABENE: In that case, your Honor, I think we should have the opportunity to test that hypoposias.

THE COURT: I think that you can. Go ahead.

MS. PENSABENE: Okay.

BY MS. PENSABENE:

04:38PM

Q. And, Dr. Mehta, you would agree that in fact anastrozole, aminoglutethimide and fadrozole studies all showed that higher tolerated doses did not provide greater efficacy?

A. That is correct.

Q. And all of that was known prior to 2000, correct?

04:39PM

A. That is correct.

THE COURT: So, would it be somewhat of a leap to use DeFriend for the proposition that you are positing?

THE WITNESS: Somewhat of a leap, yes. And I think, on the other hand, the 250 dose as Howell successfully uses it, if I were a developer at that time you finally found a

04:39PM

dose that has brought 69 percent response rate with good duration of response, you found a safety profile that is completely acceptable. Going forward into Phase III trial, I would not monkey with the dose bringing it down because I don't know if I would be hurting those women saying -- that's the whole idea of Phase II trials, you are setting efficacy and it's set on the doses which are set by the Phase I trial.

So, I think that at the end of the Phase II as you are beginning randomized trial where you tell women this is the standard of care, but half of you are not going to get it, you are going to get this new drug, why would you lower the dose of something that just worked? And what would be the justification to say I'm going to try 25 or 50 mg and see what happens why those women don't get controlled. You should have known that's probably not a very scientific way of doing research clinically.

So there is an awesome amount of responsibility to getting a dose that has actually given you safety and efficacy into the next set, and that's exactly what happened. 250 was -- went through their Phase III trials, it's just that subsequently it was realized that that was not as efficacious as they would have hoped and then 500 was cleared. So, yeah, the 500 is simply a leap of faith in terms of it's interesting that this 7-day dose actually translated to 500. But Howell, did they know that? I don't know. I wasn't part of that

discussion. But to take Howell 250 mg, which is efficacy and safety data, the only Phase II then, which everybody's now saying, so now we test it further, how would I assure a women saying I'm going to try a little lower on you because that might work? It's not a good idea. It's a new compound and laws about SERMs and AIs may not work there.

Q. Dr. Mehta, you would agree with me that the gold metal team that you talked about --

A. Yes.

Q. -- went down in dose after Howell following the Howell teachings, right?

A. Yes.

Q. Okay, let's take a look at Howell, if we could. That's at JTX-11. You'd agree with me that you selected Howell to consider because it related to hormone-dependent breast cancer?

A. Yes.

MS. PENSABENE: Your Honor, if I could, I'd like to just fill in the rest of our chart over here --

THE COURT: Okay.

MS. PENSABENE: I'm going to fill in the rest of our chart over here that's nearest Dr. Mehta.

BY MS. PENSABENE:

Q. So, let's fill in for Howell. I'm accurate if I put here under Howell "hormone-dependent," right?

A. Postmenopausal hormone-dependent, yes.
Q. And the Howell formulation was given intramuscularly?
A. That is correct.
Q. So I can fill that with intramuscularly, correct?
04:43PM A. Yes.
Q. And the Howell formulation is given every 4 weeks, once monthly, right?
A. That is correct.
Q. Okay. And in Howell the fulvestrant was not
04:43PM cross-resistant?
A. That's correct.
Q. So, you would agree with me that this chart, that McLeskey and Howell don't match in four areas that we've discussed, right?
04:44PM A. Yes.
Q. Okay. So they don't, McLeskey and Howell don't match on hormone dependence. McLeskey is hormone-independent, Howell is hormone-dependent, right?
A. Which is not a surprise, right.
04:44PM Q. And McLeskey, the formulations of fulvestrant were subcutaneous and in Howell the formulations were intramuscular?
A. Yes.
Q. So, they do not match on that either, the route of
04:44PM administration, right?

A. True.
Q. And in McLeskey the formulations were administered once weekly and in Howell the fulvestrant formulations were administered once monthly, so they do not much on dosage frequency, right?
A. Yes.
Q. And McLeskey found that the fulvestrant formulation to be cross-resistant and Howell not cross-resistant, so they do not match on cross-resistance, right?
A. Yes.
Q. Let's talk a bit more about Howell, if we could. Now, reading the Howell paper, Howell says in the paper that the patients were highly selected. Is that right?
A. Yes.
Q. And Howell also says in the paper that tamoxifen withdrawal may have accounted for the response seen in up to one third of the patients. Do you remember that?
A. He does say that, yes.
Q. Now, you just disagree with both of those things; is that right?
A. So, I have my own interpretation of that data, yes.
Q. But your interpretation is different from the interpretation of the paper?
A. Yes.
Q. And you are familiar with the fact that researchers at

the time cautioned that the Howell response rate should be interpreted with care.

A. That's always true for Phase II studies, so yes, that was said.

04:46PM Q. And you are familiar, aren't you, with the paper that Dr. Dowsett published in the Lancet about the Howell study?

A. I'm familiar with that.

Q. And let's just talk for a moment. The Lancet, that's one of the premier medical journals, right?

04:46PM A. Yes.

Q. It's like sort of the gold standard medical journal, right?

A. Yes.

Q. And Dr. Dowsett, he was one of the people that you

04:47PM mentioned as being on this gold metal team, right?

A. Yes.

Q. And what Dr. Dowsett said was, he criticized -- he said it should be -- Howell should be viewed with caution for two reasons, and one of those reasons was that Howell had included

04:47PM the no change patients in the response rate, and the second reason was that the patients were highly selected. Did I get that description of Dowsett's criticisms correct?

A. That description is correct.

Q. But you disagree with both of those criticisms by Dr.

04:47PM Dowsett that he made in the Lancet in 1995 at the time of the

Howell research?
A. I do.
Q. Dr. Mehta, you'd agree with me that the Howell study in the papers published, that Howell published in 1995 and 1996, he indicated that further research was needed to confirm the response rate?
A. That is true.
Q. And the Howell papers also indicated that further research was required to see long-term effects on bone because that was a concern, right?
A. That is true, yes.
Q. And Howell also indicated that further research was required on amount on dose, right?
A. Yes.
Q. So, those were all open questions according to the Howell paper, right --
A. Yes.
Q. -- in 1996, right?
A. Yes.
THE COURT: Excuse me. Remind me again why it's significant to you that Howell viewed no change -- why you view that to be a response?
THE WITNESS: So, there is a body of thought that -- and they were being honest, so basically said okay, we are bunching the no responses with the responses, but that may or

not be true. But the prevailing wisdom then and prevailing wisdom now is that if you have rapidly progressive disease or metabolic disease and a patient stabilizes and you have stable disease, that is counted as response. Today, drugs are approved based on a result that says patient stabilized. So it's become -- so my basic take is that while they were being very cautious in interpreting their data, I interpreted it differently. I interpreted that only progression was progression, deaths were deaths, either a woman stabilized and there was stable disease and a woman responded, they were all in the same basket.

THE COURT: And so, my question is would a person skilled in the art -- was that how a person skilled in the art would interpret those results? And, if so, then why did Howell break it down?

THE WITNESS: He's the one who reports the 69 percent response rate. By being an honest investigator, he's also listing caveats. And listing caveats in terms of this may be the reason why these results are this good is a good way of doing it because subsequent studies will basically look at that option. And if that's the reason why this happened, then that drug would probably start to lose its support. So, all Phase II studies that are at times these thoughts expressed which basically -- may look at the results and look at the -- look at the population and come up with what they may honestly

feel might have resulted in the results that were described, but in my opinion the stable disease was counted and should be counted as part of those who responded.

Q. Dr. Mehta, your interpretation is today, is that correct?

04:51PM A. That was my interpretation then.

MS. PENSABENE: Can you put up the Howell paper for me, please? If you could just enlarge that a little so we can see it.

BY MS. PENSABENE:

04:51PM Q. And what Dr. Dowsett is saying here is that the approach of including no change patients is uncommon. And that was in 1995?

A. Right.

Q. That's his statement here in 1995, right?

04:51PM A. Yes. It's uncommon but it's not unheard of. And it became over the next 15 years a dictum that everybody accepts that stable disease is good news. We tell our patients no news is good news and that's exactly what this is.

Q. Dr. Mehta, in your timeline in your pre --

04:52PM THE COURT: Excuse me. What is the exhibit number that was just up on the screen?

MS. PENSABENE: I'm sorry. That is Dowsett, it's been admitted into evidence, it's PTX-421, your Honor.

THE COURT: Thank you.

04:52PM BY MS. PENSABENE:

Q. Dr. Mehta, there's a couple other things I just want to talk about that aren't included in your timeline.

So right after Howell, you understand that four oral clinical trials with fulvestrant were conducted from 1994 to 1997?

A. Yes.

Q. Okay. But you didn't include that in your analysis --

A. No.

Q. -- right?

Another thing that's not in your timeline is the early clinical work for Thomas.

A. Yes.

Q. Now, that publication by Thomas came to the conclusion that fulvestrant showed activity in premenopausal women, isn't that right?

A. Can I see the publication?

Q. Oh, certainly.

A. Because there was a mixed conclusion from Thomas.

MR. O'BOYLE: Your Honor, may I approach?

MS. PENSABENE: May my colleague approach?

THE COURT: Yes.

BY MS. PENSABENE:

Q. This is PTX-249. And, Dr. Mehta, you'd agree with me that PTX-249, the Thomas study, that's not on your timeline. It's another seven day study, like DeFriend, that looked at

fulvestrant in premenopausal patients?
A. Yes.
Q. And Thomas concludes that the compound may be able to be used in premenopausal women based on biological activity, right?
A. Yes. If I read his conclusion, in going to the last page, the last paragraph, he basically says that fulvestrant was well tolerated during short-term use. It did not cause an increase in LH or FSH secretion and may suppress LH surge. There was no evidence of ovarian hyperstimulation although follicular growth continued.

And so he basically confirmed that in premenopausal woman using of this product would not stimulate the lining of the uterus, which we already know from other prior art. I don't interpret this article to say that there was a therapeutic response that he was basically talking about in terms of not having uterus vehicle side effects is what he's talking about. If response in terms of how hormones were affected in a premenopausal woman was something he was talking about, but there's no mention of treating premenopausal women without looks that improved because of this particular study.
Q. Dr. Mehta, do you remember having your deposition taken in this action?
A. Yes.

MS. PENSABENE: And if you could put up Mehta

transcript 163, Lines 10, I think, to 17.

BY MS. PENSABENE:

Q. Do you remember that we talked about the Thomas paper at your deposition Dr. Mehta?

04:57PM A. Yes, I do.

Q. And I asked you the following question and you gave the following answer:

QUESTION: And Thomas concludes, right, that the absence of adverse events or of evidence of ovarian

04:57PM hyperstimulation suggests that this compound may be able to be used for the treatment of estrogen dependent diseases in premenopausal women, right?

And there was an objection.

And your answer was:

04:57PM ANSWER: That's what he concludes.

Correct?

A. Right.

Q. Okay. So in terms of treatment of premenopausal women, if you could just look at your slide DDX-1-10 -- I'm sorry.

04:57PM No, 1-11. I apologize.

A. Yes.

Q. On the right-hand side of this slide you would agree with me this shows how to treat premenopausal women with endocrine therapy?

04:58PM A. It shows options available at that time.

Q. So one could treat premenopausal women with fulvestrant after using an LHRH agonist and that was known? The use of LHRH agonists were known?

A. So the understanding was that because it does not work in premenopausal women you had to convert the premenopausal woman into a menopausal female by some means so that now you will have physiology which is similar to postmenopausal and then this product would be used. So the option of using fulvestrant was always possible if the woman agreed to go into menopause.

THE COURT: Ms. Pensabene, do you have much more?

MS. PENSABENE: I don't -- of course it depends on the witness.

THE COURT: Let me ask this, were you planning on coming back in the second phase of the trial?

THE WITNESS: No. I could.

MS. PENSABENE: I can hurry up and maybe we can finish redirect.

THE WITNESS: I could come back if that's what it takes.

MS. PETERSON: He does have plans to return home and was not planning on coming back for the second week of trial. So if we could accommodate the witness, we would like to try to finish today if that's okay.

MS. PENSABENE: That's fine.

MS. PETERSON: I appreciate you volunteering but we would like to finish.

THE WITNESS: I'll speed up my answers.

THE COURT: Well, don't talk any faster.

04:59PM So let's see if we can finish him up as a curtesy to the witness.

MS. PENSABENE: Absolutely, your Honor. We'll cross a bunch of things out, Dr. Mehta.

BY MS. PENSABENE:

04:59PM Q. Dr. Mehta, you'd agree with me that in 2000, as well as today, treatment of male breast cancer follows the same principles as treatment of female breast cancer, right?

A. That's the treatment we offer, yes.

Q. And in your practice you offer hormone therapy for male

05:00PM breast cancer?

A. Yes, I do.

Q. And the paradigm for treatment of women's breast cancer just transfers to men's breast cancer, right?

A. Yes.

05:00PM Q. You know, just going back to your thoughts about this gold medal team, Dukes was on the gold medal team, right?

A. Yes.

Q. And McLeskey was not on the gold medal team, right?

A. Yes, McLeskey was an independent investigator in the

05:00PM United States, she was not part of AstraZeneca's stable of

investigators.
Q. Dr. Mehta, your focus has been on treating patients, I understand from when we've talked before, and not on researching new treatments, right?
05:01PM A. I have been involved in human research. And there is no oncology practice or person in this country that in some way or other would not participate in research because so many questions need answering.
Q. And you're not an expert on pharmacokinetics, right?
05:01PM A. No, I'm not.
Q. And you've never been involved in preclinical research, right?
A. So the American Society of Oncology 2011 presentation in Chicago was a big clinical research on a Phase I molecule
05:02PM called B28, so that's the molecule that was shepherded and subsequently it was now in Phase II trial. So in my time in the academic world I have participated in clinical studies.
Q. Let me be more precise then. Prior to 2000 you were never involved in preclinical research?
05:02PM A. During my fellowship, I was. But once I left for India, no.
Q. And you've never formulated any compounds, right?
A. No.
Q. And you don't have any experience using breast cancer
05:02PM animal models, right?

A. No.
Q. And you've never advised a pharmaceutical company on whether to select a drug for development, continue development, or abandoned development, right?
05:03PM A. No.
Q. And you've never served on a scientific advisory board on drug development, right?
A. No.
Q. And you did not publish any scientific papers prior to
05:03PM 2005, right?
A. That's correct.
Q. And you've never been involved in the selection of clinical end points for a breast cancer trial, right?
A. Yes, that is correct.
05:03PM Q. Okay. You would agree with me that breast cancer is a very complicated disease?
A. It is.
Q. And the ability to extend endocrine therapy was important because that means patients have a better chance of survival,
05:04PM right?
A. That is correct.
Q. And if you had a patient with expected life survival of six months and adding one month to survival becomes very relevant, right?
05:04PM A. True.

Q. And if you have a choice between two treatments, all else being equal, in your view that additional time to progression would be a factor in choosing between those treatments?
A. Yes.
05:04PM Q. Now, I think you and I both agree that the development of treatment for breast cancer is very difficult, right?
A. Yes.
Q. And tamoxifen, as an example, almost didn't get to the market, right?
05:04PM A. Yes.
Q. And tamoxifen took decades actually to develop into a breast cancer treatment, right?
A. That is correct.
Q. But tamoxifen saved millions of lives, right?
05:05PM A. Yes. It did, yes.
Q. So suffice it to say it was important to patients to spend that time and effort on development, right?
A. Yes.
MS. PENSABENE: I have nothing further, your Honor.
05:05PM I'll pass the witness.
THE COURT: Redirect.
MS. PETERSON: Yes, Your Honor.
(REDIRECT EXAMINATION OF DR. MEHTA BY MS. PETERSON:)
MS. PENSABENE: I'm sorry, so sorry.
05:05PM BY MS. PETERSON:

Q. Dr. Mehta, looking at the board over there that Ms. Pensabene wrote on describing Howell and McLeskey, the studies in Howell and McLeskey, were they for a different purpose?

05:06PM A. They were for different purpose, yes.

Q. And the purpose in Howell, was that to treat humans?

A. Purpose in Howell was to treat postmenopausal women with metastatic disease.

Q. And was the purpose in McLeskey to test a hypothesis

05:06PM about estrogen independent cell lines?

A. That is correct.

Q. Are there any similarities between McLeskey and Howell, in terms of the formulation that was administered?

A. The only similarities that involved castor oil base and

05:06PM they are drawn from the same source around the same time.

Q. What do you mean, drawn from the same source at the same time?

A. Most were supplied by AstraZeneca in -- around the same time, so one would feel that AstraZeneca at that time was

05:06PM testing same iteration of the product.

Q. And are there any similarities in the concentration of the drug that was delivered?

A. Similarities with what?

Q. Or the concentration of the drug that was administered.

05:07PM A. In Howell?

Q. Yes, and McLeskey.

THE COURT: Are there any similarities in the concentrations between the two?

THE WITNESS: 15-milligrams per mL was the reigning principle, so...

BY MS. PETERSON:

Q. Now, Ms. Pensabene asked you if the formulation in McLeskey was an animal formulation.

Do you recall that?

A. Yes.

Q. And, of course, the formulation in McLeskey, was that administered to animals in her study?

A. Yes.

Q. Now, would that fact dissuade a person of skill in the art from using that formulation in humans if it contained the same components?

MS. PENSABENE: Objection. Leading.

THE WITNESS: It would not.

THE COURT: Wait, wait, wait. No, I'll allow it.

THE WITNESS: It -- it would not detract from using it.

BY MS. PETERSON:

Q. Now, Ms. Pensabene also referenced the Robertson 19 -- I'm sorry, strike that. I'll start again.

Ms. Pensabene mentioned that Howell had instructed or

told people to go down in dose.

Do you recall that?

A. Yes.

MS. PETERSON: If we could pull up JTX-13, please, and go to Abstract No. 28 on the bottom right?

BY MS. PETERSON:

Q. And do you recognize this?

A. Yes.

Q. What is this?

A. This is the Robertson abstract on Faslodex versus tamoxifen.

Q. And this came after in time after -- did this come after in time after Howell?

A. Yes.

Q. At what point in time?

A. This was '99, so many years later.

Q. And what doses were being tested in Robertson?

A. 50, 125 and 250 milligrams of fulvestrant.

Q. So even after Howell, the researchers were continuing to test the 250-milligram dose, correct?

A. They were.

Q. And I wasn't sure, when Ms. Pensabene was asking about the Dukes patents, I didn't know if there was something that you wanted to clarify about your answer or if you understood.

Was there something you wanted to clarify?

A. So I think again, it's my common sense that tells me that if Duke patent, the product was available from '80s, got patients in early '90s, but subsequently if McLeskey is supplying a product in the time frame of '95, '96 by AstraZeneca's executives for testing it, then that's the product they actually been giving others who are trying to test it in humans.

And so it makes sense that that's exactly the product that brought the results that Howell describes. Why would something else be tried at two times because the results would then not make any sense.

So while it is possible that you couldn't have any product because we don't have information, common sense suggests that what formulation McLeskey lists in that time frame supplied by AstraZeneca, was the product AstraZeneca supplied its team of researchers that did the most important phase through trial for a very important product the company was in the process of developing.

So I think I would basically, as a POSA, feel that that's the leap of faith I was willing to take.

THE COURT: I was just going to ask that -- it sounds as if you have questions in your mind and you are wondering and you're speculating and -- but you're saying it could be.

THE WITNESS: Yes.

THE COURT: Okay.

THE WITNESS: It is reasonable to expect that these two products are the same. Beyond that, we don't have any data.

THE COURT: And do you agree that other POSAs may not view it quite the way you do.

05:11PM

THE WITNESS: It's possible.

BY MS. PETERSON:

Q. Just to clarify your answer there.

Was your answer -- was your opinion that that was what a person of skill in the art would understand?

05:11PM

A. Yes.

MS. PETERSON: If we could pull up defendant's demonstrative DDX-10-019.

BY MS. PETERSON:

05:11PM Q. I recall during Ms. Pensabene's cross-examination, she may have -- or she referred to -- she pulled up this demonstrative, DDX-10-019, and asked you to confirm that you agreed with her that Wakeling 1993 was telling people to conduct further tests for this unproven mechanism.

05:12PM

Do you recall that?

A. Yes.

Q. Are those words "unproven mechanism," here on your demonstrative?

A. No. Those were her words.

05:12PM Q. So you do not agree with that?

A. No.

MS. PETERSON: No further questions.

THE COURT: Okay. You get to go home.

THE WITNESS: Thank you, Your Honor.

05:12PM THE COURT: Very nice to meet you, safe travels home. Please be careful stepping down. Thank you.

MR. PRUGO: Your Honor, just one question about the boards.

THE COURT: Yes.

05:12PM MR. PRUGO: I think it's probably clear from the transcript and we don't need the boards necessarily, but do you want us to take a picture of it. How would you like us to handle a couple of the demonstratives here.

THE COURT: Well, you have the smaller versions.

05:13PM MS. PENSABENE: Of this one and --

MR. PRUGO: Well --

MS. PENSABENE: I'm sorry.

MR. PRUGO: No, go ahead, please.

THE COURT: On the chart here?

05:13PM MR. PRUGO: Yeah, exactly.

THE COURT: I think that was okay. I don't think we need a copy of that.

MR. PRUGO: And I think this verbally came out.

THE COURT: Yes, I think so, yeah.

05:13PM So a question has arisen as to the exhibits. So you

folks are welcome to leave the exhibits in the attorney conference rooms. I think Mr. Roney has checked and they are available. So you can just somehow secure them, okay?

So are we on schedule? Is it going as the parties had anticipated?

05:13PM

MS. PENSABENE: Yes, Your Honor, I think we will be able to complete on schedule.

THE COURT: Yes. Do the defendants agree, Mr. Rizzi, do you agree?

05:13PM

MR. RIZZI: I would say more or less, Your Honor. I guess one question in terms of the week of August 1st.

THE COURT: Yes.

MR. RIZZI: Is it your expectation that we would -- well, let me ask this, would you like closings?

05:14PM

THE COURT: Yes.

MR. RIZZI: In addition to post-trial briefing.

THE COURT: Yes.

MR. RIZZI: So would the closings be deferred, then, until we complete the trial on the extra couple of days?

05:14PM

THE COURT: I would like to have closings as to this portion of the trial.

MR. RIZZI: Okay.

THE COURT: And I would like to have post-trial briefing as to this portion of the trial, because we don't

05:14PM

have the date for the, quote, third portion yet, right?

MR. RIZZI: That's correct, Your Honor.

THE COURT: And so --

MR. RIZZI: But the issues do overlap.

THE COURT: They do, they do. I'm not suggesting it one way or the other that they don't, but it's all up here and I want to keep it up here as long as I possibly can. So the more that it -- that we can get much of this -- is there a reason why you couldn't do the briefing?

Is there a reason why a party might be prejudiced if I required briefing now as to all of the issues, except for the inequitable conduct?

MR. RIZZI: I guess it's hard to say in terms -- we don't know obviously what testimony will be elicited from the witnesses who haven't been deposed yet.

THE COURT: Right.

MR. RIZZI: Obviously, that's geared towards inequitable conduct.

THE COURT: Right.

MR. RIZZI: It may also be relevant to invalidity.

THE COURT: Right.

MR. RIZZI: And I can see some logic to deferring at least on invalidity and doing that together with inequitable conduct.

MS. PENSABENE: It seems to us, Your Honor, that it makes sense to do the invalidity and infringement briefing now

that we're presenting in this portion of the case, and it also could be helpful in narrowing whatever issues there might be left for inequitable conduct.

So we would think that briefing now while everything is fresh is best. One other suggestion is to do briefing and then have a short closing at a later date after the briefing, if that makes sense to Your Honor to have a time to ask questions based on the briefing. I know we've done that in some other cases.

05:15PM 05:16PM

THE COURT: Yeah, I mean, we could do that. I mean --

MR. RIZZI: Would it make sense to --

THE COURT: Mr. Rizzi.

MR. RIZZI: Would it make sense to do the briefing after August 4th and then defer --

05:16PM

THE COURT: The closings?

MR. RIZZI: -- closings?

THE COURT: Yeah. We can defer the closings, but I would like the briefing and so we can talk about dates for the briefing, but we can defer the closings and so the parties won't need to be prepared for the closings.

05:16PM

MR. RIZZI: And then, I mean, if -- depending on time the additional testimony that might come in may allow for supplemental briefing, if that's --

05:16PM

THE COURT: Right. Well, see, do the parties have a

sense as to when the third phase might occur? Because then you need --

MR. RIZZI: I think we're in the process of trying to schedule depositions in the U.K.

05:17PM THE COURT: Yeah, has that gone well?

MR. RIZZI: I don't think we have dates. We're trying to do them in September.

THE COURT: Okay. In September. Yeah. So --

MR. RIZZI: Obviously sometime --

05:17PM THE COURT: -- what we could do is maybe do the closings at that stage as well.

MR. RIZZI: Yes. I mean, assuming the depositions happen in September, what was Your Honor thinking about scheduling the last part of trial?

05:17PM THE COURT: Sometime in October, because I have a very long criminal trial in November which will go into December. So I would want to get this done, again, if the testimony is secured by then, I'd want to get this done in October.

05:17PM MR. RIZZI: Understood.

THE COURT: That's my hope. Okay.

So we will pick up on the week of August 1st. There won't be closings, and then I will talk to you folks about post-trial briefing then, okay?

05:18PM MR. RIZZI: Thank you, Your Honor.

THE COURT: Okay. So everyone enjoy some of their summer until I see you back, okay?

MS. PENSABENE: You also, Your Honor.

THE COURT: All right. Thank you.

05:18PM THE DEPUTY CLERK: All rise.

(5:18 p.m.)

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