UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION	*	16-MD-2740
	*	Section H
Relates to: 16-CV-17144	*	July 25, 2019
	*	10:00 a.m.

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ORAL ARGUMENT BEFORE
THE HONORABLE JANE T. MILAZZO
UNITED STATES DISTRICT JUDGE

Appearances:

For the Plaintiffs:
Barrios Kingsdorf & Casteix, LLP
BY: DAWN M. BARRIOS, ESQ.
701 Poydras Street, Suite 3650
New Orleans, Louisiana 70139

For the Plaintiffs:
Pendley Baudin & Coffin, LLP
BY: CHRISTOPHER L. COFFIN, ESQ.
1515 Poydras Street, Suite 1400
New Orleans, Louisiana 70112

For the Plaintiffs:
Morgan & Morgan, P.A.
BY: EMILY C. JEFFCOTT, ESQ.
700 S. Palafox Street, Suite 95
Pensacola, Florida 32502

For the Plaintiffs:
Gainsburgh Benjamin David Meunier & Warshauer, LLC
BY: M. PALMER LAMBERT, ESQ.
1100 Poydras Street, Suite 2800
New Orleans, Louisiana 70163

Appearances:

For the Plaintiffs:	DAVID F. MICELI, LLC BY: DAVID F. MICELI, ESQ. Post Office Box 2519 Carrollton, Georgia 30112
For the Plaintiffs:	Williams Hart Boundas Easterby, BY: BRIAN A. ABRAMSON, ESQ. 8441 Gulf Freeway, Suite 600 Houston, Texas 77017
For the Sanofi Defendants:	Irwin Fritchie Urquhart & Moore, LLC BY: DOUGLAS J. MOORE, ESQ. 400 Poydras Street, Suite 2700 New Orleans, Louisiana 70130
For the Sanofi Defendants:	Shook Hardy & Bacon, LLP BY: HARLEY V. RATLIFF, ESQ. ADRIENNE L. BYARD, ESQ. JON STRONGMAN, ESQ. CONNOR J. SEARS, ESQ. CHRIS MCRAE, ESQ. 2555 Grand Boulevard Kansas City, Missouri 64108
Official Court Reporter:	Toni Doyle Tusa, CCR, FCRR 500 Poydras Street, Room B-275 New Orleans, Louisiana 70130 (504) 589-7778

Proceedings recorded by mechanical stenography using computer-aided transcription software.

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PROCEEDINGS

(July 25, 2019)

THE COURT: Good morning. Are we ready to proceed?

MR. COFFIN: Yes, Your Honor.

THE COURT: The first motion we are going to deal with is the motion to exclude the testimony that relies upon defendants' employee, Dr. Kopreski.

MR. MICELI: We are moving to exclude any reliance on Dr. Kopreski's analysis.

Before we get started, Your Honor, there are a number of cases that we are going to discuss and I didn't know -- I brought copies for you. I brought copies of different documents that are cited in the briefs that relate to persisting alopecia. I could hand them up; or if you don't need them, I don't need to do that, Your Honor.

THE COURT: Well, were the cases cited in the briefing?

MR. MICELI: Yes, Your Honor.

THE COURT: We probably already have those printed --

MR. MICELI: All right.

THE COURT: -- but any documents you want to refer to, that might be helpful, unless you just want to use it on -- oh, you already have them.

MR. MICELI: I'm going to hand this up, Your Honor.

By the way, we haven't had the opportunity. I'm

10:05

David Miceli, and I will be arguing this motion.

THE COURT: Thank you, Mr. Miceli.

MR. MICELI: Is the clock ready to get started?

THE DEPUTY CLERK: It's ready.

MR. MICELI: Thank you, Your Honor. May it please the Court. My name is David Miceli, as I just introduced myself, and I'm here to discuss our motion to exclude Dr. Kopreski in his reanalysis and reimagining of some of the TAX316 information.

It starts really, Your Honor, with a series of events that begin in 2010. TAX316 was a clinical study that Sanofi conducted with a 10-year follow-up. At the end of that 10-year follow-up, after one year of putting it together, a clinical study report was completed.

The clinical study report is on the screen, Table 7 is, and you will see that alopecia ongoing -- and the testimony has been ongoing at the end of the follow-up period, that's the 10-year period -- 29 individuals (4.2 percent).

Defendant has argued or proposed that Dr. Kopreski was necessary to tease out the word "persisting" from "ongoing." However, that's not the case because in 2013 Sanofi did that themselves.

You will see in this agency request for information the EMA, the European equivalent of the FDA, requested that Sanofi provide information about long-term,

10:07 permanent alopecia, and on that point Sanofi responded that by the end of the follow-up period 29 patients (4.2 percent) still had persistent alopecia. You can see at the top of that blowout this is referring again to TAX316.

In the binder that I handed up, Item 2 is an email string that includes Emanuel Palatinsky, a medical officer in pharmacovigilance, and Pierre Mancini, who is the head of biostatistics for oncology. On page 3 of Tab 2, you will see that Emanuel Palatinsky says that for answering the question of permanent, long-term alopecia, insert the information from Table 7. That's Tab 1, and that's what I have already shown you.

In 2018 Sanofi repeated this assertion of 29 ongoing (3.9 percent). It's not necessary to explain right now, I don't believe, but there was a change in the denominator to take it from 4.2 to 3.9 percent.

For the first time in this litigation, Sanofi comes up with the explanation that Dr. Michael Kopreski, an oncologist, performs on his own a statistical re-examination of part of the study results from TAX316. It's cited in our brief, and the deposition testimony is clear he only looked at information up to and including 2004. He never looked at the long-term follow-up data.

It's important because Sanofi has to defend this case, and we are alleging that they didn't warn. There's

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something called CIOMS, the Council for International Organizations of Medical Sciences. When a percentage of incidence rate is between 1 and 10 percent, you must warn. You must warn doctors; you must warn patients.

4.2 or 3.9, whichever one we pick, falls into the clinical study report, the FDA 2018 submission -- excuse me, Your Honor -- by Sanofi to the FDA and the 2013 submission to EMA. They represent multiple times -- before this litigation ever gets started and once during this litigation -- that 3.9 percent common is the rate. However, for the first time here in this courtroom and nowhere else they find a nonstatistician, an oncologist, to come up with this 1 percent.

Why is that important? Well, one thing, the reason it's important is this is an expert opinion. We have put forth a statistician, the head of biostatistics at Columbia University, the former dean of arts and sciences, who has put together a very well-thought-out, organized report that sets out how you look at statistical measures.

The defendants have hired a statistician. They go and get a former employee, sequester him from the rest of the company -- nobody else at Sanofi has seen this, or at least there's no evidence that they have -- and he comes up with a new rate for this litigation. He is not a statistician, he didn't follow protocols, he received all of his information from counsel, and he didn't review the long-term safety

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information. Sanofi's experts just simply can't be allowed to rely upon this. It's not what experts normally rely on. It doesn't have the indicia that *Daubert* requires of reliability. When you look at what their experts tell us:

Dr. Arrowsmith, I mean, I looked at his table that he set up. I don't know who compiled the data that he reviewed.

Mr. Victoria, a regulatory individual, admits that there is no written protocol.

THE DEPUTY CLERK: You are at five.

MR. MICELI: Thank you.

He doesn't know the source of it, but he assumes it's counsel.

Dr. Glaspy is really without excuse, Your Honor, because he becomes a study investigator in August of 2005. He had to sign off on the protocols and the statistical analysis plan where he understood the meticulous nature and the detailed way to collect, validate, and analyze data. The way our expert does it is the way that Pierre Mancini, their internal head of biostatistics, does it. Dr. Glaspy knew better. He can't rely upon a small bite out of a very large chunk of data.

How did the authors of the TAX316 10-year follow-up describe it? In *The Lancet Oncology*, Dr. Mackey, who was the chief author of the 10-year follow-up publication, says that few patients were lost to follow-up, and it allows for an

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unbiased comparison of both efficacy and safety. The compliance with the protocol was high. The authors disagree with Sanofi's position in this courtroom.

Dr. Kopreski's analysis has no predefined protocol, it has limited information he reviewed, spoonfed to him by counsel, and he reaches a different conclusion than Sanofi itself has reached in 2010?

THE COURT: Has Dr. Kopreski shared the results of this analysis outside of this litigation?

MR. MICELI: No, Your Honor.

THE COURT: Was there any peer review of anything -- I mean, if he is reevaluating a case that's become part of Sanofi's study, was there any publication of this anywhere outside of this litigation?

MR. MICELI: Your Honor, there's no publication outside this litigation. There's no peer review. When I was questioning Mr. Victoria, he said that he didn't see that anybody at Sanofi had ever even seen Dr. Kopreski's analysis. It is totally for purposes of this litigation. It disagrees with how Sanofi evaluated the data in 2010, 2013, 2015 -- we will hear about that a little bit more this morning -- and 2018. Sanofi's counsel is attempting to rewrite history for purposes of the defense of this litigation.

If Dr. Kopreski is correct and the appropriate incidence rate is less than 1 percent, then during the course

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of this litigation Sanofi has submitted incorrect information to FDA. But because it hasn't been shared outside of this litigation, what we know is that for now this is Sanofi's little secret just for this litigation.

Thank you, Your Honor.

THE COURT: Thank you.

MS. BYARD: Your Honor, Adrienne Byard for defendant Sanofi.

Many people are not familiar with clinical trials, Your Honor, which is the reason why it does not surprise me that the terms of art that are used in that context are being misconstrued in the public sphere and in this courtroom.

What ongoing meant in the study was that women reported alopecia after they stopped taking the study medicine. That's all it meant, and it is no surprise to anyone here that 30 days after chemotherapy treatment ended some women said, "I still have alopecia." Those were the women that were counted if that was their last follow-up visit and that is it. It is not a study on permanent alopecia nor has it ever been represented by Sanofi to be a study on permanent alopecia.

What plaintiffs asked our witness to do was to say, "Look at the data and tell us if these are cases of permanent alopecia," and so that's what Dr. Kopreski did.

What happened, Your Honor, is that when patients

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were enrolled in the study, they were marked for 69 adverse events. If they reported any one of those adverse events, including alopecia, they were marked. They were tracked. They were kept count of.

So what Dr. Kopreski was able to do on plaintiffs' deposition notice for 30(b)(6) testimony, Sanofi's corporate position on the issue, is tell us which one of these women meet the criteria for the thing that we are all here to talk about. That's not what the early study analysis did at all. It was just counting women who said, "This is what I'm experiencing." It wasn't studying or trying to understand this phenomena that they are here to tell you exists today, which is permanent alopecia. I will look at this more closely with you.

THE COURT: You understand, Ms. Byard, this is not what was presented to the FDA. Dr. Kopreski, as I understand it, has not issued an expert report. He is not going to be called to testify. It creates a bit of a problem, if you will, and maybe we need to talk about where that problem arises in the context of this litigation.

MS. BYARD: Well, I will show you, Your Honor. We actually have done this analysis. Sanofi actually has done this analysis for outside agencies before and we will look at that.

To the extent Your Honor feels like Dr. Kopreski hasn't been discovered well enough, we have actually been

10:17 before Magistrate Judge North about the parameters and the burden that was imposed on him as Sanofi's corporate representative almost a half dozen times.

The man has sat for a deposition seven times. He has been our corporate representative three times. He was deposed for over 35 hours on the record, and there are over 2,000 pages of deposition testimony about this issue and about his analysis. So to suggest that this isn't a well-vetted opinion, it certainly is.

The real problem, Your Honor, is that the plaintiffs' experts haven't done the work that Dr. Kopreski did, and there's no reason why they couldn't. It would just take time and it would just take money. Dr. Kopreski has done that caliber of analysis. He has. That's what's different about Dr. Kopreski. He was a statistician at our company, Sanofi, for 15 years, a pharmacovigilance scientist, so he is dealing with safety data. What Dr. Kopreski adds to the equation is that he is a medical oncologist.

So when we talk about these 29 women, it's not just an "I reported it once. Count me." He traced each woman through the clinical trial for 10 years to see: Did she have this thing that we are all here to talk about? Is this permanent alopecia when she said, "I have alopecia and I'm in a follow-up period"? Was that this permanent alopecia thing, as the plaintiffs have defined it, using their definition? He

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said no, and he individually traced each woman.

This is different than what Dr. Kessler did. Dr. Kessler could have done it. He could have looked at the case report forms for each one of these women and looked at them and saw what they were experiencing and when they were doing it. He wouldn't have done it with the background of an oncologist. Dr. Madigan didn't do it either. And that's actually why we are here is that they didn't do the work that Dr. Kopreski did. They could have.

We are here because be careful what you wish for. They gave us a 30(b)(6) deposition notice. They asked for Sanofi's corporate position on the topic of what happened to these 29 women -- what happened to them -- and Dr. Kopreski sat down and he told us what happened to each individual one of them and that all but six of them could not meet this definition that they have come up with for this lawsuit.

Here is the notice, Your Honor. There's not an expert report because it's corporate position testimony. They asked for our corporate position, and what we do under a 30(b)(6) is we go to the information known or reasonably available to the organization.

We defined persistent alopecia. There's a protocol. There's pages and pages of transcript about the protocol because North has had to hear from us about it until we are all blue in the face. It's written. It's published.

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It's on PACER. We have all talked about what the parameters of this exercise would be, and we have done it for 2,000 pages of depo transcript.

THE DEPUTY CLERK: Ms. Byard, you are at five minutes.

MS. BYARD: Here's the issue, and this is what's most critical. Every single time my opponent stands up here and says Sanofi told FDA the rate was blank, the rate we are talking about is ongoing alopecia. It is not permanent alopecia. It's a rate of women that at some point when they were last followed in the study for that adverse event said, "Count me. I still have alopecia." It wasn't necessarily women who have permanent alopecia.

Plaintiffs' experts have misconstrued the data and they have said that it means that it was permanent. Every time they talk to you about the TAX316 clinical trial, they tell this Court, they will tell a jury that that rate of ongoing, "Just count me. It's 30 days after. Count me," that that means permanent alopecia, and it does not. That's how they have misconstrued it time and time again.

Ongoing, Your Honor, means that there are patients who were in the study and they had recurrence of the cancer. So their hair didn't grow back because they succumbed to the illness. That's not who we are here to talk about as far as does this medicine do this thing. It's not patients who

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succumb to the illness, whose hair never regrows because they died during follow-up.

If that woman was last seen two months after she stopped chemotherapy, she is counted for all time in Sanofi's numbers because the last time we were able to check on her she still had alopecia; but because she succumbed to the illness and she died, that isn't necessarily a rate of permanent alopecia. It's just two months after chemo. That's the best we knew, but we continued to count her. We say she is ongoing into the follow-up period. We count her.

This is what Dr. Kopreski did. He traced each one of those individual 29 women and said, "When we last checked in on you, did you have alopecia, and was that six months after chemo?" Because if it was less time than that because you died during follow-up or you decided to withdraw from the study, you are ongoing. So, sure, you're in that 4.2 percent rate of women who are ongoing, but that's not permanent alopecia. That's not what we are here to talk about.

I wish we would have known when we were working on TAX316 that this is how this data would be misconstrued. Sanofi certainly would have done that analysis, but that's not what the analysis was. That's not what anyone was saying that number meant. It's a clinical trial. Most people aren't used to it, but this term "ongoing into follow-up," that's all it means.

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Here is an example of the analysis, Your Honor, and he gives you an example of a patient. There's one patient, for instance, who is counted. She is on the list. She had to stop taking Taxotere because she had an infusion site reaction. She had a reaction to the medication. She has breast cancer, relapses, and she dies.

She is on the list of ongoing alopecia because we count her for having had alopecia when she was taking our medicine. She is on Taxol. We don't know what happens with her alopecia after that because we don't continue to follow you once you start taking another medicine.

When you look at the analysis, when you trace the women, it's just six women that meet their definition.

You had asked about publicizing this, and this is the last point that I will make. Health Canada actually asked Sanofi this very, very question. They said: Does ongoing mean permanent? Does ongoing mean that these are women whose hair didn't grow back? We explained to Health Canada -- this is the question, can you clarify what it means, and we said ongoing does not necessarily mean that those AEs were ongoing for the entire 10-year follow-up period; it just means as of their last visit it was being reported.

Now, that last visit could have been at two months post chemo or it could have been at 10 years; but if it was just at two months, you are going to be in that 29. You

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are sure not in that six, the six cases of women that we know about from this study that actually meet the definition that they gave us to answer on our corporate position.

This is all of the information that we submitted to Health Canada in 2012. That column that I'm highlighting here, that's how long the women experienced alopecia.

THE COURT: Okay. I think we're probably beyond, so I'm going to give Mr. Miceli extra time.

MS. BYARD: Perfect.

THE COURT: I'm not a statistician, so I'm almost afraid to ask this question.

MS. BYARD: That's fine. I'm not either. We will do our best.

THE COURT: Okay. This is something that I find particularly troublesome. We have this group of 29 women that had ongoing alopecia --

MS. BYARD: Yes, ongoing.

THE COURT: -- some of whom died --

MS. BYARD: Right.

THE COURT: -- within the six months.

MS. BYARD: Yes.

THE COURT: So now it's 28 women --

MS. BYARD: Exactly.

THE COURT: -- who have persistent alopecia. Are they part of the original number? Because it seems to me that

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gets a little skewed. Do you see what I'm saying? So if you have 100 women -- let's make it easy because I went to law school for a reason.

MS. BYARD: Same.

THE COURT: Okay. We have 100 women that are in your study. At the conclusion of two months, 10 have ongoing alopecia and then two die. So you say we have 100 in our group. Eight have persistent alopecia. Isn't that a bit skewed? Because you are still counting in the 100 those two that we can never know if it was going to be persistent. So does the number go back and now we have 98 and, of that 98, eight have persistent alopecia?

MS. BYARD: It's actually fairer than that because we don't drop them out of the 10.

THE COURT: What?

MS. BYARD: We don't drop them out of the 10.

THE COURT: So they stay in --

MS. BYARD: We counted them as 10. They stay at 10 even though they passed away. We keep counting them.

THE COURT: So it stays 10 if they have changed treatment because there's been a recurrence or they die --

MS. BYARD: That's exactly right.

THE COURT: So the only way they are removed from the 10 is if their hair returns to where it was before?

MS. BYARD: While we are still following them,

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absolutely right.

THE COURT: Within that six months?

MS. BYARD: Yes. If at their last follow-up visit they had alopecia, we are still counting them. We are counting them when we are doing the analysis in 2005. We are still here talking about them today.

THE COURT: We are counting them as persistent?

MS. BYARD: We are counting them as persistent. We are counting them as ongoing into the follow-up period. They were in the follow-up period. They had alopecia at their last visit. They are counted. They are part of that 29, and they stay there for all time.

THE COURT: Okay. So they are now persistent?

MS. BYARD: They are persistent. Their last follow-up visit --

THE COURT: Okay.

MS. BYARD: Yes.

THE COURT: I have to tell you, I was having trouble.

MS. BYARD: No, absolutely, and that's why it's fair and that's why it's reliable. Any one of their experts could do what Dr. Kopreski did. It's going to take a lot of time and it's going to take a lot of money to get there, but any one of them could do it.

The data is the data. It's not a reanalysis. We weren't studying permanent alopecia. We weren't. We didn't

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know that this would be how the data would be misconstrued. We were asked about it in a lawsuit for a 30(b)(6) deposition:

"What is Sanofi's corporate position on this issue?"

We go, "That's not what the data is. That's not what those 29 women are. They are just as of the last time we saw them they had alopecia."

THE COURT: You understand the difficulty with having Dr. Kopreski's reanalysis. I understand what you are saying is that he sat for a 30(b)(6) and he was deposed. He is going to issue new opinions that are now going to be relied on by other experts, but he is not going to be called as an expert.

MS. BYARD: He is a corporate representative. He is not a lay witness. That's not fair.

THE COURT: Right.

MS. BYARD: He is a fact witness and he is a corporate representative.

THE COURT: And he will be testifying.

MS. BYARD: I think that remains to be seen on how the case comes in. Some of this stuff we have said they shouldn't be able to confuse the jury about to begin with.

THE COURT: Right, right, right. Okay.

MS. BYARD: Thank you, Your Honor.

MR. MICELI: Your Honor, we have been going for a little while. Can I have some rebuttal time?

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THE COURT: That's what I said. I'll give you a little rebuttal time.

MR. MICELI: Thank you, Your Honor.

THE COURT: We have a lot to do today.

MR. MICELI: We do have a lot to do, Your Honor. I will be very brief.

THE COURT: Okay.

MR. MICELI: I can help you understand this. If you look at Tab 1 of that binder that I handed up to you, what Ms. Byard had explained about what ongoing in the follow-up means, if you start at line 1 that says "Alopecia" and you move across, there's a number that you come to. The column is headed "Ongoing."

THE COURT: Right.

MR. MICELI: Excuse me, not "Ongoing." "Persisting into follow-up." That's 687 women. That's the number of woman who had alopecia at the end of the 31st day after their last treatment. That represents the number of women who enter follow-up with alopecia.

THE COURT: Right. Right.

MR. MICELI: The 29 has been compiled pursuant to the protocols that were written back in 1997. The plaintiffs did not come in and decide how this study was going to be conducted and how you would count those 29 women. What I would encourage Your Honor to do is look at Dr. Kopreski's second volume of his

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deposition, Exhibit 39, and it lists the 29 individuals and how long they had their alopecia ongoing.

If you look at -- I believe it's either Tab 8 or 9. I don't have my binder in front of me because I don't want to fumble through papers while I'm standing here. If you look at that, it's a series of emails that begins with one from Camille Vleminckx from the EMA. She mentions to Sanofi that at the end of the 10-year follow-up, with an average follow-up of these 29 women of 8.7 years, that Sanofi should consider those 29 women as being permanent and irreversible alopecia. That's how the regulatory agency looked at it. The data was collected the way Sanofi decided it would be collected, not the way we decided it would be collected.

She says Dr. Kopreski did this tremendous work. He did some quick work. He gave a deposition in September, the end of September, and he gives another deposition in the beginning of December, and we are not told that he does this. This is sprung on us at a deposition within a week of when the defendants give us their expert reports. So we realize in this deposition that their experts -- we learn five days later that their experts relied upon something that we didn't learn about until just a few days prior.

Our deposition notice does not define what alopecia is. Magistrate Judge North did not define for all time what alopecia would mean. There was an agreement as to

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how they would collect data. Please read the deposition notice because what it says is we want to talk to you about the people on this chart and what you used to compile this chart. It was their chart, their people. We didn't ask them to do anything. We certainly didn't request the post hoc, litigation-driven, spoonfed-by-attorneys analysis that Dr. Kopreski did.

So he is not an expert, didn't give us a report, we learn about it at the last minute before we have to start preparing to depose their experts, never published, not peer-reviewed, and it is not the type of evidence that experts in the statistical field -- he is not a statistician. He is doing the job in one month's time or two months' time that a team from Sanofi -- we heard this throughout this litigation, a multidisciplinary, cross-functional team from Sanofi in a third-party research organization called the Breast Cancer International Research Group (BCIRG). It's on all the documents. A team of statisticians, epidemiologists, and doctors put together the TAX316 report, and one man who is not a statistician comes in and takes one bite out of a very large bundle of information and says, "I have figured this out, but let's keep it a secret for this litigation."

THE COURT: Thank you.

MR. MICELI: Thank you.

THE COURT: Mr. Lambert.

MR. LAMBERT: Yes, Your Honor. We are ready to

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proceed on the second motions?

THE COURT: Yes.

MR. LAMBERT: I'll try to keep this one short.

Good morning, Your Honor. Palmer Lambert from Gainsburgh Benjamin on behalf of plaintiff. May it please the Court.

Plaintiff, Barbara Earnest, seeks exclusion of the supplemental opinions of doctors Shapiro and Smart regarding stem cells. To make it clear, we are not seeking exclusion of these experts' original general and case-specific reports. The reason we did not seek exclusion of those initial opinions, although we disagree with them, is that they related to the analysis of tissue biopsies through medically accepted and reliable dermatopathology staining. That's H&E staining.

However, the supplemental opinions submitted by Dr. Shapiro and Dr. Smart regarding stem cell staining and its alleged impact on diagnosis of permanent chemotherapy-induced alopecia: (1) lack any indicia of reliability; (2) have no foundation in science; and (3) are contradicted by their own deposition testimony.

First, Dr. Smart agrees with Dr. Thompson that the IHC (immunohistochemical) stains cytokeratin-15 and Ki-67 are nonspecific and they stain more than just follicular stem cells. Dr. Smart makes no attempt to differentiate the particular types of follicular stem cells from other stem cells

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and other cells that she acknowledges to be present in the scalp tissue.

Dr. Shapiro's supplemental opinion purports to ascribe meaning to the, quote, positive CK-15 and Ki-67 staining, yet his deposition testimony says, in response to the question of what it means:

"I would have to defer to a dermatopathologist. I'm a dermatologist, not a stem cell expert. I'm not a stain expert. This is not what I do. I have never ordered that test in over three decades."

Dr. Smart's supplemental opinions also are contradicted by her deposition testimony. Her opinion states that because the stem cells in the bulge region are present that Ms. Earnest doesn't have permanent alopecia. Well, in her deposition testimony she says there's no established evidence in the literature to state whether or not -- and I'm paraphrasing -- stem cells being present or absent have anything to do with permanent chemotherapy-induced alopecia.

Dr. Smart further undermines her opinion with this additional statement that if she had thought those stains would add or subtract from her initial diagnosis, she would have used them. This question and answer suggests that she didn't think they were needed in her original report.

I have this slide in here about the *Pipitone* case. An equivocal opinion does not make any fact more or less

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probable and is irrelevant under the Rules of Evidence. Dr. Shapiro admitted he is unqualified to offer opinions on stem cells. Dr. Smart has testified that the stem cell staining, positive or negative, does not have anything to do with permanent chemotherapy-induced alopecia. These opinions do not make any fact more or less probable.

In conclusion, Your Honor, in the PSC's collective years of practice, we have never seen expert reports that lack a single citation to medical or scientific literature and, on top of that, experts who completely contradict and walk back those unsupported opinions. For those reasons, Ms. Earnest respectfully requests that the supplemental opinions of doctors Shapiro and Smart be excluded from trial.

Unless Your Honor has questions, I'm through.

THE COURT: I don't think so.

Mr. Sears.

MR. SEARS: Good morning, Your Honor.

THE COURT: Good morning.

MR. SEARS: Connor Sears. It's nice to meet you.

Your Honor, what plaintiffs are doing here is they are moving to exclude evidence that they paid their experts to create. It was very expensive testing and it's testing that their experts, if it was favorable for them, would have relied on, included in their reports, and included in their analysis. They paid for it, it turned out to be bad for

10:38 them, and so now they are trying to disregard it and claim it's unreliable.

There's really two points that Mr. Lambert brought up that I want to respond to. The first is the reliability of cytokeratin-15 testing and the Ki-67 testing, and the second is Dr. Smart and Dr. Shapiro's ability to rely on the testing and offer expert opinions about it. So let me start off by giving some background how all this came to be.

I have deposed Dr. Tosti and Dr. Thompson. Dr. Tosti is a dermatologist and Dr. Thompson is a dermatopathologist. So one of the issues in this case is, well, their claim is that Taxotere causes ongoing alopecia, so how does that happen? What's the mechanism of action?

So I asked Dr. Tosti that, I asked Dr. Thompson that, and both of them said, "Well, it's hypothetical, but we think the mechanism of action is that it somehow damages or kills the stem cells in a very specific region of the hair follicle called the bulge region, and by doing that it causes ongoing alopecia."

So what happened very early on in this litigation is --

THE COURT: We are not going there again, the video and -- go ahead. I'm sorry. I just don't want to go over the same ground that we go over pretty much every month.

MR. SEARS: I understand.

10:39

So what happened is Dr. Tosti, their dermatologist, and Dr. Thompson, their dermatopathologist, exchanged some emails. Dr. Tosti said, "Well, let's take some biopsies and let's test them for stem cells," and so that's what Dr. Thompson did.

I asked him, "Whose idea was it to do the staining?"

He said, "it was my idea."

THE COURT: Right.

MR. SEARS: He is the one who choose the cytokeratin-15 and the Ki-67.

THE COURT: Right.

MR. SEARS: So I deposed him and I asked him, "Well, why did you choose cytokeratin-15?"

What he said is, "It's the only investigational antibody that I have experience with that works."

So this is their own expert saying that "I chose cytokeratin-15," which is an immunohistochemical stain that's used to detect whether stem cells are present in the bulge region, and he did that because it works.

THE COURT: Does the fact that this testing was negative somehow or another prove that this wasn't chemotherapy-induced alopecia?

MR. SEARS: It's kind of a --

THE COURT: I'm just trying to figure out, what does

10:40

this testimony give us?

MR. SEARS: I understand.

THE COURT: We have three people that were tested. I don't think we can say that that's a study. Are you telling me that the fact that this testing produced negative results somehow says that the alopecia suffered by Ms. Earnest is not related to chemotherapy? Just tell me, what does this give me?

MR. SEARS: I understand.

THE COURT: Bottom line.

MR. SEARS: Bottom line. Okay. There's two things:

One, it proves that the mechanism of action, if that's correct, it's not chemotherapy because the stem cells are present, the stem cells are not damaged, and they are proliferating. So if their mechanism of action theory is that chemotherapy kills the stem cells, then this shows that can't be true.

The second thing is that if the stem cells are present, hair loss is not permanent. The stem cells are what causes the hair to grow. If the stem cells are there, the hair loss can be reversible and the hair can still grow. So that's why it's relevant to this litigation.

THE COURT: So when is it permanent?

MR. SEARS: Hair loss is permanent if the stem cells are not present. If the stem cells have been damaged, then the hair follicle couldn't regenerate and could not grow.

10:42

THE COURT: So are those cases that were dismissed because of statute of limitations -- I'm just trying to figure out when we figure out when is it permanent. If they can regrow, what -- go ahead.

To me it's a bit of a difficult place that we find ourselves because what I'm hearing is six months post we consider that persistent, not permanent. If there are stem cells present, then it's not permanent. How long is this claim open for and when do we decide it's permanent? Do we have to test for stem cells and as long as there's any stem cells --

MR. SEARS: Hair loss is very multifactorial, so it's difficult to say when hair loss is permanent. Generally speaking, there's two types of hair loss. There's nonscarring and scarring hair loss.

THE COURT: Right.

MR. SEARS: Scarring hair loss is when the follicle is no longer present, and that's permanent. Nonscarring hair loss, in theory, is reversible.

That's kind of interesting in this case because Ms. Earnest never took any sort of drugs or tried anything to regrow her hair. There's something called minoxidil, and you can either take it by pill or you can apply it to your head. If she did that, because the stem cells are present, the hair could regrow. We just don't know because she never did that.

So ultimately it's relevant because this goes to

10:43 their mechanism of action theory, which their experts still intend to talk about, and it shows the stem cells are there, so the hair loss is not permanent.

So back to the reliability point, we have their own expert, their dermatopathologist, Dr. Thompson, saying he chose cytokeratin-15 because it works. We also know from -- there's another point I wanted to make. Not only did he know that it works, but he validated it in his lab before using it on Ms. Earnest. He got the stain in, he tested it on something else to make sure it worked, and then he used it on Ms. Earnest's pathology. So he chose it because it worked, he validated it to make sure it worked, and then he used it. It shows it's reliable.

There's more emails and more testimony from Dr. Thompson that shows that if the tests came back showing that the stem cells were not there, damaged or killed, they would have used it in the reports and would have used it in their opinions.

So he wrote: "In the event that the cytokeratin-15 findings do not add to the information, I will issue my reports without the information." The clear implication is if it helps their case, they would have included it.

So I asked Dr. Thompson about that during his deposition:

10:45

"QUESTION: So the cytokeratin-15 tested positive in Ms. Earnest's tissue?

"ANSWER: Yes."

And by "positive" it means the stem cells were there and proliferating.

"QUESTION: You wrote because it tested positive you did not pursue this further, right?

"ANSWER: That's right.

"QUESTION: If it tested negative, you would have pursued it further?

"ANSWER: Yes."

So basically what's going on is these experts conducted this testing for their mechanism of action theory. If the test results were good for them, they would have relied on them, would have included them in the reports. But it's bad for them, it disproves their mechanism of action theory and shows that the hair loss is not permanent, and so they are saying all of a sudden, "It's not reliable. We can't rely on it."

So the second thing I want to talk about is their claim that Dr. Shapiro and Dr. Smart are not qualified to talk about this.

Dr. Smart, she is a board-certified dermatopathologist. She was deposed and she was asked about this, and she said that she has the qualifications to read

10:46

cytokeratin-15 stains. She testified that she reads Ki-67 stains almost daily, which are the proliferation staining. Dr. Shapiro is a board-certified dermatologist.

It's interesting to talk about that and then compare it to their experts. Dr. Tosti is also a board-certified dermatologist and Dr. Thompson is a board-certified dermatopathologist, and so think about that. If these tests came back favorable for them, they would have had their experts, who have the same qualifications as our experts, rely on them and talk about them. But because it hurt them and it's not helpful for their case, they are saying that our experts don't have the ability to talk about that when they have the same qualifications.

Mr. Lambert, I think, mentioned that Dr. Shapiro and Dr. Smart both said that they are not experts in stem cells, but think about what a pathologist does. A pathologist looks at tissue, and they identify the tissue and the underlying disease process or mechanism that might be occurring in the tissue.

THE COURT: Sure.

MR. SEARS: They diagnose cancers, but they are not an expert in the underlying cancer. Their job is to look at the tissue and make the analysis, which is what they did here.

The interplay between Dr. Smart and Dr. Shapiro is consistent with how dermatologists and dermatopathologists

10:47

work together. The dermatopathologist reads the slide and prepares a report, which is what Dr. Smart did, and sends it to Dr. Shapiro to rely on, which is what happened here.

Mr. Lambert also -- there's a few points I wrote down when he was talking. He said it can stain other cells, and so I asked Dr. Smart about that. It can stain other cells, but what you are looking for is a pattern of staining. There's a very specific region, the bulge region. While it can stain the other cells, you can still tell that the stem cells are present based upon the pattern of staining. So it's kind of a red herring.

He also mentioned the case about equivocal opinions. Dr. Smart and Dr. Shapiro's opinions are not equivocal. They are saying --

THE COURT: I'm sorry, what?

MR. SEARS: He talked about a case saying equivocal opinions --

THE COURT: Oh, okay. I just couldn't hear you.

MR. SEARS: Sorry. I mumble sometimes.

Here their opinions are not equivocal. They are saying definitively that the stem cells are present and proliferating based upon these stains.

So the bottom line is this is testing they paid for. It was very expensive testing. They paid for it because they thought it helped their case.

10:48

THE COURT: I got that. I don't mean to cut you short. I've heard that a lot. Okay.

MR. SEARS: Well, I'll sit down, then. Thank you.

THE COURT: Thank you.

Briefly.

MR. LAMBERT: Very, very short, Your Honor, three quick points based on Mr. Sears' argument.

THE COURT: What about Mr. Sears' argument that if there are stem cells proliferating, this is not permanent hair loss or persistent hair loss, whatever we call it?

MR. LAMBERT: Your Honor, I will direct back to this slide, and I have cited the record documents, deposition testimony.

Dr. Smart agrees that the tests are not reliable in terms of what these stains are actually showing, and what counsel is assuming is that the present cells or the positive stains are support for the conclusion when there's no scientific support for that.

What you don't see in the expert report, I think, is very important. You don't see Dr. Smart saying, "I see follicular stem cells." She just says she sees stem cells.

The fact is that cytokeratin-15 and Ki-67 are nonspecific. They stain a bunch of things. Ki-67 stains anything that's growing, not necessarily a stem cell.

Your Honor, the fact that we paid our experts --

10:50

THE COURT: I don't want to talk about that.

MR. LAMBERT: -- it's a red herring.

THE COURT: I really don't want to talk about that.

MR. LAMBERT: I will move on, but --

THE COURT: Good. That's a good idea. Well, you know we have talked about that in multiple motions.

MR. LAMBERT: Ad nauseam.

THE COURT: Ad nauseam.

MR. LAMBERT: Yes, Your Honor.

THE COURT: So I don't need anybody to remind me.

MR. LAMBERT: One of the things that Mr. Sears mentioned was that he would have proceeded further. Well, Dr. Tosti says that for the biopsies of three patients to be meaningful for anything, they would have to be part of a thousand-person study with controls and whatnot, and it's simply not there.

And the fact that there is a mechanism of action theory, that one of those theories is stem cells doesn't mean that these stains are somehow reliable. There's just no scientific support for it. All of the experts agree that the stem cell mechanism of action is theory, and it's been theory since the 1990s.

Your Honor, I think that completes it unless you have additional questions.

THE COURT: No, I'm good.

10:51

MR. LAMBERT: Thank you, Your Honor.

THE COURT: Can I get you all to come up here, whoever is arguing.

(Off the record.)

THE DEPUTY CLERK: All rise.

(Recess.)

THE DEPUTY CLERK: Court is back in session. You may be seated.

MR. MCRAE: My name is Chris McRae and I represent Sanofi. I'm here today to discuss Sanofi's motion to exclude the testimony of Dr. David Madigan.

THE COURT: Thank you.

MR. MCRAE: Thank you for your patience, Your Honor.

THE COURT: No problem. Thank you for yours.

MR. MCRAE: I'm here to argue Sanofi's motion to exclude the testimony of Dr. David Madigan.

Dr. Madigan performed three different analyses in his work on this litigation and the same fundamental flaw underlies all three of these analyses, and that is simply he didn't check his work. He never actually looked to see if the cases he was identifying doing these analyses were actually cases of a medical condition at issue in this litigation, permanent or irreversible alopecia following chemotherapy.

I'm going to start by talking about Dr. Madigan's analysis of the FDA database. Dr. Madigan went

11:07

into the FDA database and he had three search criteria. He had three things he was looking for.

The first thing was he was looking for a report involving Taxotere or docetaxel. Fair enough. We don't have any quibble with that.

Then he was looking for, as the adverse event, a case of alopecia, and there is where the trouble starts because he was not searching for cases of permanent or irreversible alopecia. And he couldn't because the FDA database actually doesn't allow him to perform such a search.

So instead he had to search for alopecia and after that create this novel third search criteria where if an outcome listed on the report was "disability or permanent damage," Dr. Madigan would say, "Well, okay. It's an alopecia report. There's a box checked on the form that says 'disability or permanent damage.' I'm going to call that permanent or irreversible alopecia."

Now, the problem is -- and we will actually see an example of this in a second -- that Dr. Madigan admits that there can be multiple adverse events listed on one of these forms, meaning you can have a report of alopecia and then a report of numerous other medical conditions.

Dr. Madigan also admits that there's nothing in the report tying an outcome of disability or permanent damage to alopecia. You might have that box checked on the form, you

11:08

might have 10 different adverse events listed, but there's nothing you can do looking at FDA's database to say, "Aha. I know that 'disability or permanent damage' is actually talking about alopecia."

Now, importantly, Dr. Madigan can't point us to anything that says this is the right way to search in FDA's database for cases of irreversible or permanent alopecia. He can't point us to a learned treatise. He can't point us to a scientific publication. He can't point us to FDA guidance that says this is the right way to do it.

Now, that being said, Dr. Madigan found 31 cases that meet this criteria, but what he didn't do was ever actually look at those cases to see if this was actually a case of permanent or irreversible alopecia. That's what we are going to do right now.

This is a MedWatch report, meaning this is a form in the FDA's database, and this is the same database that Dr. Madigan was searching. We see here it's a report of docetaxel, so Dr. Madigan's first search criteria is met. It involves the right medicine.

We see here that it reports as an adverse event alopecia. You can also see here it reports 10 or 11 different adverse events including, I believe, fatal lung cancer. Again, it's a report involving docetaxel, alopecia, so we have met Dr. Madigan's first two search criteria.

11:10

And then finally we see on the report here the box next to "disability" is checked along with a number of other outcomes, meaning this report itself meets all three of the criteria Dr. Madigan used in searching FDA's database.

What Dr. Madigan didn't actually do is look at this report to see what it's actually saying, to see if this was a case of permanent or irreversible alopecia following docetaxel use. When you actually do that, you see that this patient for the first time received docetaxel in October 2002 and received it again in December and then passed away by the end of 2002.

This is a report of a patient three months after docetaxel who had alopecia and then who passed away. There isn't an expert in this litigation who would say alopecia three months after chemotherapy use constitutes permanent or irreversible alopecia, but this is one of the cases Dr. Madigan counted. That's exactly what he is saying. He is saying, "I can tell that there's a relationship between docetaxel and irreversible alopecia on the basis of a report like this," hair loss three months after using the medicine.

The same thing is true for Dr. Madigan's search of the Sanofi adverse event database. Again, he looked for reports of alopecia and then he looked for these keywords. He ran a keyword search, basically, looking for these words or variants thereof, so "permanent" or "chronic" or "persistent."

11:11

Again, Dr. Madigan never actually looked at his search results. He never actually looked at one of these cases to see, "Well, my search hit on this, but is this actually a case of permanent or irreversible alopecia?"

When you actually do start looking -- this is from Sanofi's internal database. This is a report from it. You see here it's alopecia involving docetaxel use, so we have met that search criteria.

Then you see on the next slide, when you actually read the narrative of the report, it actually says that the hair loss had resolved and his hair has been growing back. But then in the next sentence it says, in talking about a different adverse event, that adverse event had persisted. That's why Dr. Madigan's search identifies this report, because of that word "persisted," but it's not even talking about the alopecia. It's talking about an entirely different adverse event, and yet again this is evidence that Dr. Madigan uses to establish a relationship and that's simply inappropriate.

THE DEPUTY CLERK: You are at five minutes.

MR. MCRAE: The last thing Dr. Madigan did was he reviewed Sanofi's clinical trial data. Dr. Madigan admits that the Taxotere clinical trials only looked at ongoing and not permanent alopecia, and yet again he didn't review any of the underlying data to determine if the cases he was relying on were actually cases of permanent or persistent alopecia,

11:13

meaning he relies on this patient here from the TAX316 study, this patient who first received docetaxel in August 1998. Then November 2, 1998, at her first follow-up visit, she had alopecia, but she was put on another chemotherapy medication and she was no longer followed for her alopecia.

So, again, we have three months of data. This patient took docetaxel, had alopecia from August to November, and Dr. Madigan is relying on this as evidence that Taxotere causes permanent or irreversible alopecia. But, again, no expert in this litigation would say hair loss three months after taking docetaxel means it's permanent or irreversible.

I just leave you with this quote from the *Accutane* judge in the New Jersey litigation who, after reviewing Dr. Madigan's work there, concluded that Dr. Madigan was "an expert on a mission."

Well, the same thing is true here. Dr. Madigan was looking for a relationship between Taxotere and permanent alopecia, and he crafted analyses in order to find that relationship. That analysis is unreliable and relies on, frankly, irrelevant data that doesn't have anything to do with permanent or irreversible alopecia, and for that reason his opinion should be excluded.

THE COURT: Thank you.

Mr. Abramson.

MR. ABRAMSON: Thank you, Your Honor. Brian Abramson

11:14

for the plaintiff. May it please the Court.

So I want to first direct the Court's attention to what Sanofi is not criticizing here. They are not disputing Dr. Madigan's qualifications, his expertise, his experience, and they are not contesting the general acceptance of the methodologies he used. Rather, all of their arguments are basically conflating the role of a biostatistician, what Dr. Madigan was hired to do, and how to apply the scientific, peer-reviewed methods that he employed in this case. They went through the three analyses. I would like to talk about each of those as well.

The first is this FAERS database, the FDA's adverse event reporting database. Your Honor, this is a spontaneous reporting system, so it collects electronically millions of adverse events. There are certain algorithmic methods. They are called disproportionality analyses. They have been developed because drug companies and regulators, they use these on a daily basis to survey drug data, to try to look for new safety signals and potential new concerns. That's what Dr. Madigan did here. He looked and he tried to analyze whether and, if so, when a safety signal existed within the FAERS database.

Now, Sanofi's concerns, they raise two primary ones: (1) about the search parameters; and (2) about him not looking at the underlying case reports.

11:15

First, Your Honor, these issues have come up in every case in which Dr. Madigan has done a FAERS analysis, every one. With respect to the FAERS analysis, they are always denied and here's why. One, with respect to search parameters, yes, it's true, there is no single predefined term for the words "permanent alopecia." I guess, according to Sanofi, we throw our hands up, we end the inquiry right there, and that's it. That's not how this works.

Dr. Madigan went to Dr. Kessler, the former FDA commissioner, and asked for his input on what the best and most reasonable way would be to identify cases of permanent alopecia within the database. Dr. Madigan relied on Dr. Kessler's input and he ran that search.

This is very similar to exactly what Dr. Madigan did in the *Rheinfrank* case -- which involved Depakote and developmental delay, where there were multiple search terms and multiple outcomes to look for -- and in the *Yaz* case -- we cited both these in our papers -- where they actually looked at 94 different adverse events to look for venous thrombosis. He relied in part on experts, regulatory experts, just like he did here.

Regarding the review of specific underlying case reports, that's not only inappropriate, it would be impractical. Sanofi is just focusing on the disproportionality analysis part, which is the numerator. So a disproportionality

11:17

analysis looks at the foreground, which is the numerator, and then the background, which is the denominator.

So Sanofi would have us just look at the foreground. But, in reality, to do what they want, you actually have to look at all of the background reports too, all of the adverse event reports, probably tens of thousands of case reports that identify alopecia with all other drugs because that's what it's being compared to. Clearly, you can't do this. Even if you could, you need a FOIA request. These are not publicly available documents, and that goes to the point of what this analysis is for. It's not even contemplated.

So before moving on, I also want to address the *Fosamax* case, which is also cited in our papers. The same two issues were brought up. Multiple search terms were used in that case, and the defendant there also raised the issue of Dr. Madigan's analysis is not reliable because he didn't look at the case reports. The court there rejected both of the arguments, and I'm going to quote. It says:

"This argument is inappropriate on a *Daubert* motion. Dr. Madigan's testimony will be subject to cross-examination, and the credibility of his opinion will be ultimately determined through the adversarial process. Dr. Madigan's methodology is sufficiently reliable because it is generally accepted in the scientific community and,

11:18 therefore, plaintiffs have satisfied the second prong of *Daubert*."

The same reasoning applies here. FAERS analysis was developed as a quantitative method. It doesn't call for a qualitative, subjective analysis by a biostatistician. He reasonably applied these standards, and Dr. Madigan found a signal with Taxotere starting in 2000, getting stronger with more conservative estimates over the years. It was unequivocal and, except for one brief exception, it lied exclusively with Taxotere as opposed to the other comparator drugs.

I'm not going to spend much time on the pharmacovigilance database. Frankly, Dr. Madigan relied on three other experts to define the terms because his role is not to say what it is. Sanofi disagrees with those terms. That's understandable. They did their own analysis in 2011 and 2015. They chose those search terms. That's subject for cross-examination if they don't agree with those terms.

With the clinical trial data, yes, Dr. Madigan analyzed TAX316 and 301 both individually and together. Sanofi takes issue with the fact that they say TAX316 didn't track permanent alopecia, it didn't isolate Taxotere, and then they claim that Dr. Madigan shouldn't be able to rely on TAX301 because he said it was unreliable.

Ironically, Sanofi's 2015 clinical review cited to both TAX316 and TAX301, and they concluded the data was

11:19

evidence supporting a causal association between Taxotere -- not the combination TAC -- and permanent alopecia as opposed to any other descriptor. That's their words.

Let me address these critiques, though, anyway. One, with respect to the combination, both arms of TAX316 and 301 looked at TAC versus FAC. They both have AC, so it's comparing the causal affect of T versus F.

THE COURT: Right.

MR. ABRAMSON: With respect to the permanent alopecia, the reality is there has to be some cut-off period that can be reasonably applied. Otherwise, there's no way to measure it. It's kind of what Your Honor alluded to earlier with Mr. Miceli.

Finally, Dr. Madigan never criticized TAX301 as unreliable. What he said is that because Sanofi failed to follow up with almost 80 percent of the study centers, the results of the study were small and they were underpowered, which is exactly why Dr. Madigan performed a meta-analysis. The point of a meta-analysis is to take results from multiple trials, some which may be small and underpowered, to obtain a more reliable result.

If you look at the levels of evidence hierarchy pyramid, at the very top is a meta-analysis of randomized controlled trials. That's exactly what he used here. This is far from litigation-driven. It's the gold standard.

11:20

THE DEPUTY CLERK: You have passed five minutes.

MR. ABRAMSON: Thank you.

Let me just finish up. If Dr. Madigan did what Sanofi claims he should have, his methodologies would have been inappropriate and his opinions would actually be far less reliable. He is an expert biostatistician. His role is to take available data as it existed and perform quantitative statistical analyses to assist the trier of fact in evaluating that data. That's what he did here. If anything, the criticisms lodged by Sanofi simply go to the weight, not the admissibility of this evidence, and are more appropriate for cross-examination and for the jury's consideration. For those reasons, Your Honor, we would ask the Court to deny Sanofi's motion to exclude Dr. Madigan.

THE COURT: Thank you.

MR. MCRAE: Your Honor, two points on rebuttal, if I may.

So counsel for plaintiff started off by talking about Dr. Madigan's qualifications. I would posit to you that the entire reason we have gate-keeping, the reason we are having this hearing today is to prevent otherwise qualified experts from getting in front of a jury and offering opinions that are unreliable or not relevant to the case. That's exactly what is happening here. Dr. Madigan's qualifications don't matter. What matters is what he did in this situation.

11:21

THE COURT: Right. There are two findings I have to make, he is qualified to say it and whether or not his methodology --

MR. MCRAE: Sure. We don't quibble with Dr. Madigan's qualifications.

The second point I would say is that counsel for plaintiff said that the FDA database review that Dr. Madigan performed is generally accepted, and he quoted you some cases where that has been admitted. I would say in response to that that this case is distinguishable because, again, of the search criteria Dr. Madigan had to concoct in order to find cases of irreversible alopecia.

He had to search for alopecia, and then he had to find situations where there is a box checked on the form that is permanent or disabling. In none of those other situations did Dr. Madigan, in those other cases, have to do such a search. He could actually search for the medical condition at issue in the FDA database. He couldn't do that here, and that's why this situation is different.

That's all I have. Thank you, Your Honor.

MR. RATLIFF: Good morning, Your Honor. Harley Ratliff on behalf of Sanofi. Is the Court ready?

THE COURT: I'm trying to get my notes.

Okay. Thank you. I was getting my notes out.

MR. RATLIFF: Thank you, Your Honor. I'm here to

11:23 discuss the purported expert opinion of David Kessler, who is plaintiffs' regulatory and labeling expert, although probably should be better discussed as a, quote, causation expert.

The key opinion that we are here to challenge, Your Honor, is this. Dr. Kessler's opinion is that in 2009 Sanofi should have added some type of warning regarding irreversible alopecia to a specific section of the label, what's known as the warnings and precautions section. Dr. Kessler will call that the big "Capital W" warning. That is Dr. Kessler's opinion. That is what we are here to challenge.

Now, why did Dr. Kessler pick 2009? Why did he settle on 2009 as the date by which Sanofi should have put this warning in the warnings and precautions section? He did that because that was the date he was directed to do by plaintiffs' counsel to slip in under the wire of our three bellwether plaintiffs, Antoinette Durden, Tanya Francis, and Barbara Earnest, who were diagnosed or treated with Taxotere in 2009, 2009, and 2011.

Your Honor, one, that is the hallmark of a litigation results-driven opinion, but implicit in that opinion -- and you will hear more about that in two weeks when we talk about preemption. Implicit in Dr. Kessler's opinion that this label should have been updated in 2009 is that for the 3,000 other women who were treated before 2009 with

11:24

Taxotere who are plaintiffs in this litigation, the label, per Dr. Kessler's opinion, has to have been adequate.

The other part about Dr. Kessler's opinion which I think is important to understand as we talk about his methodology -- because that is where we have the real problem -- is that Dr. Kessler's opinion that there should have been this warning in the warnings and precautions section in 2009, Your Honor, is an artificial construct that is divorced from what has happened in the real world.

At no point in the 23 years that Taxotere has been on the market has the FDA ever made the same determination that Dr. Kessler did, that there needed to be a warning in the warnings and precautions section of the Taxotere label. FDA did not make that determination in 2015 when they requested a minor update to the Taxotere label based on the exact same data that Dr. Kessler looked at. FDA did not make that determination that there needed to be a warning and precaution about permanent alopecia in 2018 when the label was updated.

In fact, not even in Dr. Kessler's seven years at FDA, when Taxotere was under his remit and responsibility, was there ever a suggestion that there should be a warning and precaution, one of the highest warnings that can be made in a label, about irreversible alopecia.

So what Dr. Kessler wants to do is say, "In my world," in this hypothetical world, "there should have been

11:26

this warning in 2009." Whereas in the real world with FDA, the agency that is responsible for the label, this has never happened.

How does Dr. Kessler get there? How does Dr. Kessler got to this particular opinion? Well, to get to that opinion, Your Honor, he has to go through methodological gymnastics to reverse engineer a date in time that best fits the facts of the particular plaintiffs in this litigation or for these bellwether plaintiffs, which is now just down to Ms. Earnest, and he does this by doing a seven-factor test which he takes from the FDA guidance.

Dr. Kessler, per his own words, says, "I have to reach the substantial majority of these factors." Here are the two problems with his analysis and his methodology -- because we are not just challenging his ultimate opinions just being wrong, but the methodology being right. That would be subject to cross-examination. We are talking about his methodology and how he got here.

Factor 6, he has no evidence about that. We can take that off the radar.

For three of his other factors, Dr. Kessler relies on data and analysis that occurs after 2009, a 2018 article, a 2017 article, a 2014 article. Your Honor, courts time and time again have said you cannot take post-injury data to impose a duty on a defendant pre-injury. For factors 3, 4,

11:27

and 5, that is the type of data that Dr. Kessler relied on to get to his opinion, post-injury data that wouldn't have been available to either Sanofi or FDA at the time he says a label should have been updated.

So what about the remaining three factors? For the remaining three factors -- and plaintiffs make a point of this in their opposition -- they say, "Well, there was pre-2009 data." Let's talk about that pre-2009 data.

The real problem is Dr. Kessler has taken a definition of permanent alopecia which he says, per plaintiffs' complaint, is partial or incomplete hair growth six months from chemotherapy. Your Honor, we have no quibble with that definition. That's the definition they have chosen, although Dr. Kessler readily concedes that there will be numerous cases that fall outside of his definition. Hair may regrow after six months. He says when you are talking about a year-plus, that's when you start talking about irreversibility. Because he recognizes that his hard cut-off has some wiggle room, I think, Your Honor, that imposes on Dr. Kessler an obligation to do a more thorough investigation to see if his narrow definition meets the data sets to which he applied it to. These are the data sets that plaintiffs talk about.

GEICAM 9805, one of the big clinical trials you are going to hear a lot about at this trial, there plaintiffs' experts concede that the data from there says that all of the

11:28

9.2 percent of ongoing alopecia cases were 31 days after chemotherapy. What Dr. Kessler does not know and what Dr. Kessler did not endeavor to do is to figure out which of those patients, if any, had alopecia that met his definition. He does not know that.

The same with TAX316, which we talked about with Dr. Kopreski. Dr. Kessler recognized that he would need to know the last date of the follow-up visit when alopecia was reported. Was that last follow-up visit at two weeks? Was it at two months? Was it at six months? Was it at five years? Was it at ten years? That would be the only way for him to take his definition of permanent alopecia and apply it to that data. Dr. Kessler did not do that.

The remaining two options would be the FAERS analysis, and that's what Mr. McRae just talked about. Dr. Kessler takes Madigan's analysis. He does nothing further than what Madigan did. He looks at the numbers. He doesn't pop the hood on what those numbers mean and whether those cases actually meet his definition of permanent alopecia. So he takes his definition, applies it to data, but doesn't do the next step of the analysis, Your Honor, to see if those cases -- those cases of what he calls permanent alopecia -- actually meet his definition of permanent alopecia to meet his remaining factors. When you think about that methodology, Your Honor --

Well, one other thing. The last point here is

11:30

the plaintiffs rely on in their opposition that Dr. Kessler testified at his deposition that he could rely on a single two-paragraph abstract of 2016 called the Sedlacek abstract. If you look in his report, Your Honor, Dr. Sedlacek is mentioned one time, buried in this footnote, without any discussion from Dr. Kessler about its relevance, its importance, or how it meets any one of his seven factors.

So when you take those pieces of evidence and that methodology, the unreliable application of a definition to the data sets he relied on, you can take out 1, 2, and 7. None of the substantial majority of factors are met when you look at his actual methodology.

Did he actually do the work to make sure that his definition of permanent alopecia met the data sets that he applied them to, which would get him to this idea that there should have been a label change in the warnings and precautions section in 2009 -- which did not happen then and has not happened as we sit here today despite the fact that, to step back just a second, FDA had GEICAM 9805, they had TAX316, they had their own adverse events, and they had Sanofi's adverse events. Based on that same data, FDA has never reached the same conclusion that Dr. Kessler would like to come in to the jury and tell them about what should have happened versus what really happened.

This gets to the last point, Your Honor, I want

11:31

to make. This is an important point, which is Dr. Kessler testified time and time again he is not here as a specific causation expert, that he is not qualified, nor is he giving a medical causation opinion, Your Honor. But what we have seen in these litigations and what I can assure you we will see in this courtroom is that Dr. Kessler will come in under the auspice of giving regulatory opinions only to try to insert causation opinions to supplant the causation analysis of the jury.

If you look at his report, Your Honor, and if you look at his deposition, it is replete with not just a regulatory causation -- a reasonable possibility of a causal association, which is a regulatory term at a lower level -- his testimony is replete with causation opinions.

So on one hand he wants to disclaim those opinions; on the other hand, he wants to come in and couch those opinions in terms of a regulatory opinion to be able to get that into evidence. That is the type of testimony that will be confusing and prejudicial to the jury.

It is also the type of testimony that has been regularly precluded by other similar experts trying to do the exact same path, which is to give a regulatory opinion, but implicit in that opinion is actual causation testimony. That's why Dr. Kessler is on their will-call list and their causation experts, Dr. Madigan and Dr. Feigal, are on their may-call

11:33

list.

So, for example, this is what Dr. Kessler says in his deposition, Taxotere is the causative agent. "It's Taxotere. That's the causative agent here."

Your Honor, that is not regulatory testimony. That is someone trying to give a causation opinion couched under the rubric of being a regulatory opinion.

So our challenges to Dr. Kessler are two parts: (1) the methodology that he used to try to kind of create this artificial world; (2) the fact that if he is allowed to come in and talk about reasonable causation, causal association. That is going to lead the jurors to rely on him as the causation expert for plaintiffs, and courts time and time again have said they are not going to allow that.

Now, Dr. Kessler, we are not fussing with his qualifications. There's no doubt he worked at the FDA. Plaintiffs spent five to six pages of their opposition touting his qualifications even though we didn't spend any time challenging them.

So if Dr. Kessler wants to come in and explain the complex regulatory scheme related to FDA, how that works, how labeling works, we are not here to challenge that Your Honor. What we are here to challenge is the idea that he can insert the opinion that Sanofi should have done something that FDA never did. That is why his opinion should be

precluded both in terms of his unreliable methodology but also the prejudice and confusion it is going to cause the jury.

In fact --

THE DEPUTY CLERK: You are at 11 minutes.

MR. RATLIFF: Okay.

This is Dr. Kessler's own words: "Some people confuse that with causation." That is why his opinion should not come in.

Thank you, Your Honor.

THE COURT: Thank you.

Ms. Jeffcott.

MS. JEFFCOTT: May it please the Court. My name is Emily Jeffcott. I'm here on behalf of plaintiffs.

Your Honor, I'm a little frustrated. I spent this weekend preparing from Dr. Feigal's *Daubert* opposition only to have it taken off on Monday, and then in this argument just now I heard a number of arguments that pertain to preemption. Preemption is not at issue. That will be argued in a few weeks. Specifically, what the FDA knew and when and the Sedlacek argument, those were both raised in terms of the preemption motion, and I prepared for Dr. Kessler's *Daubert* opposition. So those other arguments we will reserve until that time.

Your Honor, defendants' motion to exclude Dr. Kessler's opinions in this case should be denied.

11:35

THE COURT: Let me ask, is Dr. Kessler giving causation testimony?

MS. JEFFCOTT: No, Your Honor. Dr. Kessler has explicitly stated that he is not. Sanofi objects to Dr. Kessler giving medical causation testimony but also to his opinion about a causal association. That's one of the points that I wanted to raise.

To opine regarding the adequacy of a label, his overarching opinion that the Taxotere label should have included a warning about permanent alopecia requires that predicate opinion regarding causal association. FDA guidelines and FDA regulations state to provide a warning there must be reasonable evidence of a causal association.

Now, contrary to Mr. Ratliff's statement, they do challenge his qualifications regarding his ability to give that causal association testimony. As we know, Dr. Kessler is the former FDA commissioner. He is a medical doctor, the former dean of two medical schools, a lawyer. He is perfectly qualified to opine on matters of causal association as it pertains to the regulatory construct.

Indeed, he has offered this type of opinion about causal association before. In the *Actos* case, he opined there that bladder cancer should have been warned of in the Actos label, and that considered that causal association predicate opinion. It's a necessary, to reach that opinion

11:37 whether or not there's a causal association, in order to opine on, too, that larger opinion regarding the adequacy of the label.

In the briefing they cite to a number of cases against Novartis. Well, those were specific to Dr. Parisian. In those cases Dr. Parisian was found not to be qualified based on her own experience and then also based on the analysis, the methodology that she applied. For instance, one thing that was cited is that she merely mentioned that there was literature supporting a causal association and that the clinical trials also supported those causal associations without going into depth as to why.

In this case Dr. Kessler has gone through in his report to explain how the medical literature, as you saw the references to the medical literature, and also how the clinical trials and Dr. Madigan's analysis all pertain to the issue of causal association.

I want to put something up. Mr. Ratliff states that Dr. Kessler didn't rely on pre-2011 data. That 2011 date is the year that Ms. Earnest was treated. Well, to the contrary, the scientific literature supported and Dr. Kessler's report has multiple, if not many, instances of literature establishing the relationship between permanent alopecia and Taxotere.

The same things for Sanofi's own clinical trial

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data -- the TAX316, TAX301 -- the pooled analysis done by Dr. Madigan, as well as the FAERS and the internal pharmacovigilance databases that Dr. Madigan also reviewed. All of those have pre-2011 data that establish a relationship, that causal association between Taxotere and permanent alopecia.

Sanofi also takes issue with Dr. Kessler's definition. Your Honor, quite frankly, I was a little bit confused by Sanofi's argument. In their original brief, Sanofi seemed to complain that Dr. Kessler didn't apply a consistent definition, that he had multiple definitions going on, and then in their reply brief -- and Mr. Ratliff kind of cleared this up -- it's more about the six-month definition.

I think what I'm going to start out with is there isn't really a Dr. Kessler definition, and I think what would be good is to look really at how he defined it in his report. I'll zoom in.

Dr. Kessler looked at multiple sources for the definition of permanent alopecia, and here we start with the medical literature. The medical literature, based on Dr. Kessler's review, was consistent to show that six months equated with permanent alopecia. But as Sanofi correctly pointed out in their reply brief, there is other medical literature out there that says a year, two years is, in fact, sufficient for that determination of permanent alopecia.

11:40

Among all the definitions present, Dr. Kessler went with six months from the medical literature. However, he also looked at the definitions provided by Sanofi internally, and that was four years by Dr. Palatinsky, which is Sanofi's global safety officer. In addition, Sanofi reported in their safety report -- which I believe was provided to multiple regulatory agencies -- that alopecia is persistent at 12 months, and then in 2015 Sanofi used two years. So Dr. Kessler considered multiple definitions.

In fact, in his analysis of the incidence rates of permanent alopecia, he didn't just apply six months. He considered these multiple definitions to ensure that the reliability of his analysis was consistent no matter how you defined it, and that's the point. When he looked at it using six months, a year, two years, 55 months, eight years, ten years, it all came back to a sufficient incidence rate to warrant inclusion of a warning of permanent alopecia in the Taxotere label.

Now, there's one final point I would like to make, Your Honor. Ms. Byard brought this up in her initial arguments regarding whether or not Dr. Kessler had the capability to look at each individual case report to assess whether or not it should have been included, but the reality is under a proper methodology you don't do that.

Specifically, FDA guidance says when you are

11:42

looking at adverse reaction rates, when you are looking at the incidence rate, you don't want to go through and look at each individual entry because that introduces bias and inconsistency in the results. You look at it at an objective level without going to that root cause analysis.

THE DEPUTY CLERK: You are at about eight minutes.

MS. JEFFCOTT: Your Honor, for those reasons, defendants' motion to exclude Dr. Kessler's *Daubert* motion should be denied.

Thank you so much.

THE COURT: Thank you.

MR. RATLIFF: Your Honor, may I address two quick points? Under a minute.

THE COURT: You have already had about 15 minutes.

MR. RATLIFF: One minute. Two minutes.

THE COURT: Twenty seconds.

MR. RATLIFF: Your Honor, everything Ms. Jeffcott said didn't address the fundamental issue we have with Dr. Kessler. Ms. Jeffcott referenced, well, he actually used lots of definitions or he looked at lots of definitions, but she never talked about did he reliably apply those definitions to the data set to determine if those data sets met his definitions.

She also said, well, he reviewed a lot of clinical trials. We have no dispute that Dr. Kessler reviewed

11:43

those clinical trials. Our challenge, Your Honor, and the underlying of our challenge is what he did not do was take those clinical trials and apply them to his definition to make a determination to get to his ultimate opinion that a change in the label should have happened in 2009, a warnings and precautions change, which has never happened and has never been mandated by FDA.

Thank you, Your Honor.

THE COURT: I think we have two causation arguments. I need to go get my binders in the back, so we will be at recess for a couple minutes.

THE DEPUTY CLERK: All rise.

(Recess.)

THE DEPUTY CLERK: Court is back in session. You may be seated.

THE COURT: Mr. Strongman, give me a minute.

MR. STRONGMAN: Take your time.

THE COURT: Ready.

MR. STRONGMAN: Are you ready to proceed?

THE COURT: I am. Thank you.

MR. STRONGMAN: Your Honor, Jon Strongman on behalf of Sanofi. I will be arguing Sanofi's motion to exclude plaintiffs' proposed expert testimony on general causation.

In this case the plaintiffs do not get to take general causation for granted. They must put forward a

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specific expert witness or witnesses on this issue, those witnesses must put forward specific and reliable evidence, and they must do it by a reliable methodology. The particulars matter.

In this case the plaintiffs have tried to patch together an after-the-fact general causation opinion from two witnesses. The first is Dr. Madigan, who is a safety signal statistician. The second is Dr. Feigal, who plaintiffs have put forward as an informed consent witness. Both of these experts -- both of them -- stated that they weren't even specifically asked to address general causation within the scope of their expert report. Think about that. In this litigation, when you look through all of the expert reports that the plaintiffs provided, you couldn't even tell who plaintiffs' general causation experts were.

THE COURT: Mr. Strongman, in Louisiana are they required to show general and specific causation, or is it sufficient in Louisiana to show specific causation and then whether or not there's a causal analysis for purposes of FDA compliance?

MR. STRONGMAN: Your Honor, I would point you directly to a case that I think provides a road map to a lot of the issues that I want to talk about today, and that is the *Burst* case.

So the *Burst* case was decided right here in this

11:52 Court by Judge Vance. The *Burst* case involved an analysis as to whether or not benzene in gasoline caused the plaintiff's cancer. What Judge Vance stated was under the law plaintiff must show: general causation, that gasoline containing benzene can cause AML; and specific causation, that defendants' products caused Mr. Burst's AML.

So the answer to your question is yes. In fact, what Judge Vance went on to say is that the court may only admit specific causation evidence after the plaintiff had produced admissible evidence on general causation. That is why the particulars matter. That is why, under *Daubert*, the Court must delve into those particulars: who are the witnesses; what are their qualifications; what do they rely on; and what methodology do they use? When you delve into the particulars in this case, what you see is that plaintiffs cannot meet their burden.

So the *Burst* case which I just referenced sets out a process for doing this, and it includes two steps. The first is to identify an association between an agent and a disease, and then the second is to go through a process to determine whether or not that association is causal, which here we call the Bradford Hill criteria.

In this case the plaintiffs have not identified one single epidemiological study showing a statistically significant association between Taxotere and permanent

11:54

alopecia. Not one. Even assuming that an association could be established -- which it cannot -- not one of plaintiffs' two experts that theoretically are opining on general causation has applied any kind of Bradford Hill criteria in a methodology that's set out in a report that's understandable and that is explained. They simply didn't do their work.

When you look at the *Burst* case, what the plaintiffs were left with there is very similar to what the plaintiffs are left with here, which is case reports, it's clinical studies with statistically insignificant results, and it's ultimately with an expert that manipulates the data by combining it together. The *Burst* court said that that is unreliable and that that must be excluded.

I want to touch on these two witnesses briefly. We have heard about Dr. Madigan, and I think some context is important here. My partner, Mr. McRae, argued about Dr. Madigan's opinions regarding safety signals. When you look in these databases, when does a safety signal pop up? That's a statistical analysis. What Mr. McRae and what the lawyers arguing Dr. Madigan's motion were not talking about is general causation.

So we don't quibble with Dr. Madigan's qualifications as a statistician, but he is not a medical doctor. He is not qualified to give a general causation opinion. This issue has been addressed specifically by a court

11:56 just in the last year. So while we can argue about the FAERS analysis, about the statistics, when it comes down to really knowing is there a causation issue here, a general causation issue here, Dr. Madigan cannot carry that water.

He is a man of statistics, not medicine, and just as the court here said: "Defendants argue that Dr. Madigan lacks the medical knowledge and experience to offer a general causation opinion. The Court agrees." Again, this is just within the last year.

The plaintiffs, with regard to Dr. Madigan, regularly say, well, what he did was quantitative: numbers. What he didn't do was qualitative: quality, substance. While that may work for a signal-type analysis -- we argue it doesn't. But while that may be one way to go about it, when you get to general causation, the quality matters, the substance matters, and the particularities matter. What we know is that Dr. Madigan did not do that work.

When you look at his expert report, he sets out the questions that he was asked. They are all safety signal questions. They are not causation questions. He was specifically asked:

> **"QUESTION:** You were not asked, for example, to investigate whether docetaxel causes irreversible alopecia?
>
> **"ANSWER:** Not specifically."

11:57

But yet the plaintiffs, trying to fill a void that they realized that they had, went through with Dr. Madigan his three pieces of data. You have heard about these three pieces of data already, the two databases and the clinical trials. So with regard to the two databases, Dr. Madigan readily admits that these are merely --

THE COURT: Who was that?

THE DEPUTY CLERK: The people listening.

THE COURT: Okay. Would you please put your phones on mute.

Hello? Would you please put your phones on mute.

Please proceed, Mr. Strongman.

MR. STRONGMAN: Thank you, very much.

So with regard to the two databases that Dr. Madigan looked at, what he readily admitted is that these are not causation pieces of evidence. Do these alone demonstrate causation? No. No. He admits that. These are for safety signals. They are really not causation evidence. So two of the three pieces of data that Dr. Madigan analyzed he realizes and admits are not causation evidence.

So he is stuck with the clinical trials, and we have talked some about the clinical trials. What's important is -- again, not for safety signal, but for causation -- what do these clinical trials look at? They do not isolate

11:59

Taxotere, for one. We know that.

When you look at the *Burst* case, this is addressed. Specifically, Judge Vance stated that a study that notes that the subjects were exposed to a range of substances and then nonspecifically notes increases in disease incidence can be disregarded when you are looking at a specific --

THE COURT: Weren't the two studies dealing with TAC and FAC -- I'm not going to try to pronounce all of the --

MR. STRONGMAN: I'm with you.

THE COURT: Okay. We can say the ACs were given to both populations --

MR. STRONGMAN: Correct.

THE COURT: -- and the only difference was whether or not they were administered Taxotere in conjunction or the other medication.

MR. STRONGMAN: Correct. Correct.

THE COURT: Does that not at least -- it seems to me that you are isolating Taxotere.

MR. STRONGMAN: Well, let me give you a couple of examples on this. Okay?

THE COURT: Please.

MR. STRONGMAN: So I want to set aside the whole ongoing alopecia versus is that really persistent. We have talked about this. Let's just set that aside.

THE COURT: Let's just talk about the populations, if

12:00

you will.

MR. STRONGMAN: So at most what that study would show you, assuming that it's looking at permanent alopecia -- which we don't believe it does, but assuming it is. At most what that study is telling you it that it may happen more in one population exposed to T versus a population exposed to F.

THE COURT: Right.

MR. STRONGMAN: When you look at general causation -- and, again, Judge Vance talks about this in her opinion in *Burst*. When you do epidemiology for general causation, what you are looking for is an increase in your exposed group over the incidence in the general population.

What we have here is absolutely no evidence about the incidence rate of what we are calling permanent alopecia in the general population. So you are not comparing apples to apples for general causation purposes with these clinical trials; you are merely comparing one chemotherapy regimen to another.

I just want to give you a hypothetical. I'm not saying this is factual, but let me give you a hypothetical. Let's say that in the population irreversible hair loss or permanent alopecia occurs in 10 percent of people. We know it occurs for a whole host of reasons with many women.

THE COURT: Right. Right.

MR. STRONGMAN: Let's say it occurs in 10 percent of

12:01 people. What we see in the clinical studies, even going by plaintiffs' misguided definition, is that it's occurring in 9 percent or 4 percent. That could theoretically be less than the general population. We don't know. So the point is the plaintiffs have not done their work to actually put forward clinically significant data that shows any statistical increase when you are exposed to Taxotere when you get the outcome of permanent alopecia. It simply isn't there.

The other point that's really important for this also is that when you look at the clinical studies -- this is a quote out of the *Burst* case as well. It's my favorite case today.

THE COURT: I see that.

MR. STRONGMAN: What the Court had to say was that studies that do not represent statistically significant results may not provide a foundation for general causation.

So when Dr. Madigan did his analysis on the Taxotere clinical trials -- so we have TAX316 on the one hand, we have GEICAM on the other -- both were clinically not shown to have a statistically significant result. They were statistically not significant.

What we know from *Burst* is under the Fifth Circuit law, which is what we are operating under here, you cannot use a clinical study with a result that was not statistically significant to prove general causation. So even

12:03

if you take it to the step that comparing the T to the F has some value, it was not statistically significant.

So what Dr. Madigan then did, he said, "Well, all right. That's not going to work for me. So what I'm going to have to do is I'm going to have to combine the data. I'm going to have to put it together." The plaintiffs are calling this a meta-analysis, a pooled analysis.

What we also know from the *Burst* case is that the expert there combined the data to get a statistically significant result where one didn't already exist, and the court said you can't do that. You have to have a reason to combine data. You can't get an F on one test, get an F on another test and say, "Well, when I combine them, I get an A." It doesn't work that way in science. This was Dr. Madigan's admission, "not statistically very impressive." That's what we are dealing with.

The other point I wanted to make on this, too, with regard to Dr. Madigan, he has a lot of criticisms of the GEICAM study. He doesn't like it. He thinks it was poorly done, follow-up was not accurate. He has a lot of criticisms of it, but yet he takes it and he pools it together to get his result that he needed.

Well, in the *Accutane* litigation, he had an opportunity to do that too. If he had pooled them together, he would have gotten a result that was unfavorable to the

12:04 plaintiffs. What do you think he said? "I can't do that because when you combine two studies, I bring with it the flaws and the biases, etc." So he is doing it here; he won't do it there. What we know is that the court there said, again, this is an expert on a mission that wants a particular conclusion, period. That doesn't work in science, and it doesn't pass muster under *Daubert*.

Briefly on Dr. Feigal -- I know I'm using up my time. Dr. Feigal likewise did not offer a general causation opinion in her report. What she had to say was -- here's her scope. This is about informed consent. This is what she was asked to address, discussions between physicians and patients in light of the information available on hair loss and Taxotere.

When she was asked in her deposition, "Well, are you giving a general causation opinion?" she says she thinks it was implied in her interactions with the lawyers that she would be able to talk about this. General causation is a threshold matter. It is a critical matter. It is not one based on expert implications. Implications alone are not enough.

So the data that Dr. Feigal looked at and ultimately in her deposition had to put forward as any kind of support for a missing general causation opinion in her report were these. She looked at studies in the literature, but yet she admitted that those studies alone can't prove causation.

12:06

She admitted that.

"You would not reach a conclusion that Taxotere caused permanent alopecia just by looking at the studies and the literature in the table that you put forward?"

She said, "I think from my own opinion, yes."

What we also know is that when you look at Dr. Madigan, their other general causation expert, he was asked, "Did you review the public medical literature?"

He really didn't, but he said, "My understanding was that there were only case reports in the literature."

"Have you reviewed any of those?"

"I may have seen them. Individual case reports are not that terribly useful."

So Dr. Madigan, on the one hand, didn't even bother to look at the studies because they were not useful, and yet it's one of the three-legged stool, if you will, that Dr. Feigal puts forward. There is an internal contradiction between the plaintiffs' two experts.

The next thing that I am sure Mr. Miceli is going to stand up here and talk about is Sanofi's own internal 2015 clinical overview analysis. So what they say is that Dr. Feigal didn't exactly rely on Sanofi's conclusion in this document but how they came about it. Repeatedly, in every brief that you see, the plaintiffs cite this document, this 2015 clinical overview document, and in it you have to

12:07 understand the context.

So the clinical overview document was dealing in the regulatory context with a question of labeling, and we just heard the argument on Dr. Kessler, the exact same reality here, which is: Is Dr. Kessler offering a general causation opinion? The answer is no because he is talking about labeling in this regulatory context.

So was Sanofi offering a general causation opinion when they are talking about the same regulations that Dr. Kessler is in their internal document? The answer to that is no, they were not. How do we know that it doesn't pass muster? Again, I'm going to quote from the *Burst* case.

So in the *Burst* case what we had were various regulatory agencies that had chimed in on the issue, and this is what the judge said: "As noted by the Fifth Circuit, regulatory bodies apply a lower threshold of proof in determining issues of causation than 'is appropriate in tort law,'" and they cite the *Allen* case, which is a Fifth Circuit case. Regulatory bodies, lower threshold of proof on causation than is appropriate in tort law, and that's what we have here.

When you look at the documents that the FDA actually has -- we cited them in our briefs and in our expert reports. When you actually look at what the FDA said about our 2015 clinical overview, this is what they said: "It is impossible to determine whether the permanence of alopecia was

12:09

due to docetaxel." That is the clinical reviewer of the FDA, "impossible to determine." When you have a situation where it is impossible to determine whether or not there's a causal link, you ultimately have to rule that that evidence is inadmissible in tort.

The last leg that we have for Dr. Feigal is again the Taxotere GEICAM clinical trials.

She was asked, "Do you even know if there is a statistically significant difference in the two arms?"

She said, "I have not done that analysis. You might go ask the biostatistician."

So how can Dr. Feigal rely on clinical data when she doesn't even know if it's clinically significant or statistically significant? She can't, and we know that based on the Fifth Circuit law.

So the last thing that Dr. Feigal does is falls back on what she calls the weight of the evidence. She says she triangulated it. I don't know what that means, but it sounds to me like the *ipse dixit* of an expert who says, "Because I look at it, I feel like it's enough" -- the weight of the evidence without any methodology -- "I'm going to say I think there's causation," but courts have spoken about the weight of the evidence.

This is from the *Mirena* decision just in the last year as well, another MDL. What that court said is that

12:11

if you are going to use the weight of the evidence, you have to go through each step of it to show us why and how; because if you don't, methodologies like the weight of the evidence are "virtually standardless" and "unacceptably manipulable."

We know that the methodologies that the plaintiffs used were standardless, they were manipulable, and they were manipulated. They took what they viewed as unreliable evidence in the literature, unreliable evidence in the databases, unreliable evidence in the clinical studies -- because they weren't statistically significant -- and they jammed them all together. When you jam together three pieces of unreliable evidence, you don't somehow get a reliable opinion. You just don't. The plaintiffs did not do their work here.

We know -- again, this is out of the *Burst* case, citing a Seventh Circuit case -- that this Court has an obligation to delve into the particulars. It has an obligation to eliminate scientific guesswork. And while there may be sympathies involved -- there always are -- in this courtroom the law lags science.

If there is no epidemiological evidence, there is no proof that Taxotere causes permanent hair loss based on what the plaintiffs' experts have done, our motion must be granted, sympathies aside, because that's what's required under *Daubert*.

12:12

Thank you, Your Honor.

THE COURT: Thank you.

Mr. Miceli.

MR. MICELI: Thank you. Your Honor, if I can, I want to get a little bit situated here before I get started. I had a feeling --

Are you ready to get started?

THE COURT: I am.

MR. MICELI: Thank you. I had a feeling we were going to hear about the *Burst* case, and we can talk about that. I want to start, however, with the *Accutane* case, where they cited some criticisms of Dr. Madigan. What they failed to do is inform the Court that the 2015 case was overruled in 2017. So the criticisms, as they are, were the court's. It has been reversed.

The *Burst* case, I want to start off with -- and I'm going to get into my argument that I planned for seven minutes, but I'm assuming it will be a little longer, as my opponent's was.

THE COURT: Well, causation I anticipated would take a long time.

MR. MICELI: Thank you. Thank you, Your Honor.

The *Burst* case is easy to distinguish from this case. The *Burst* case is a benzene case. It involves a gentleman that worked in a car garage, and he was trying to

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relate the benzene exposure in gasoline to his AML leukemia.

THE COURT: Right.

MR. MICELI: The court there said, look, there are a lot of solvents that are in a shop. You're ripping apart brakes. There's oil changes. There's other fluids. There's other exposures. In that case the expert that they tried to put forward looked at all these different exposures to different chemicals and said this is the one.

We don't have that here. One thing that *Burst* does not have that we have the benefit of in this case is that we have two randomized controlled trials that, as the Court correctly pointed out, distinguishes one difference between the two populations, Taxotere and fluorouracil. I practiced that, Your Honor.

THE COURT: Well, I got as far as Taxotere that I can --

MR. MICELI: Right. So we have a randomized controlled trial, and the key word there is randomization. When you put two populations and compared them one against the other, the only difference was one got T and one got F and that's it.

Now, Mr. Strongman says, well, we don't know what the background rate is because it's against another comparator. Well, it's unethical. Sanofi's own witnesses say you cannot take a study and do one and give one person

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chemotherapy and one person nothing when they have cancer. That is simply unethical. So the best evidence is this randomized controlled trial T against F and that's it.

So with the benzene cases -- and there's a number of them that they cite in their brief. It's like benzene on parade, I think. It's a very different chemical. It's a toxic tort case where people are exposed to a multitude of chemicals in a noncontrolled setting, and then their expert comes in and says, "I'm going to lump all toxic substance A through Z together. I'm going to say because these toxic substances cause problems, my opinion is benzene -- the one in the gasoline, not the benzene in these three others -- caused this person's injury." That's 180 degrees from what we have in this case. We have a controlled study that isolates two variables, Taxotere and fluorouracil, and that's why it's important.

Mr. Strongman points out the TAX316 is not statistically significant standing alone, neither is TAX301, the GEICAM study, but it's appropriate -- and I'm going to jump around in my presentation. I apologize, but I feel I need to address these things right up front.

This screen, Your Honor, summarizes when it's most appropriate to do a meta-analysis. That first bullet point, "Meta-analysis is most appropriate when used in pooling randomized experimental trials because the studies included in

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the meta-analysis share the most significant methodological characteristics, in particular, use of randomized assignment of subjects to different exposure groups," that is exactly what we are dealing with here, precisely what we are dealing with.

When I talked to the clinical trial manager, Ms. Kim Bassi, we compared the TAX301 and the TAX316 protocols. They are virtually the same study. One study measures the effect of the drug, the safety and efficacy of the drug in women who have node-positive early stage breast cancer; one is node-negative.

Other than that, you have a population of women who were randomized -- and, again, we went over this earlier this morning when we talked about how the clinical authors described -- the published authors on the TAX316 study, what they say is that -- and I'm sorry, Your Honor, I didn't have it in this PowerPoint, but I'm going to read to the Court again that because patients who have been lost to follow-up is low -- roughly .5 percent per year in treatment group, which allows for unbiased comparisons of both efficacy and safety -- there is no doubt that this trial was not designed to try to hurt women and try to take their hair from them. It was designed in order to see if this drug worked to help women's cancer not to reoccur after they have had surgery to remove the cancer from their body.

They predefined that they would track not just

12:19 alopecia, but whether or not alopecia was reversible. This is the statistical analysis plan that was done -- I may be mistaken, Your Honor, but I think this is 2002. It's in our brief.

2002, before the follow-up period ever ended, Sanofi decided -- and they committed to writing that the reversibility of certain adverse events will be analyzed -- and this is quoted out of a deposition so you see the line numbers, Your Honor -- and the very first one listed is alopecia. The head statistician, the worldwide, global head of biostatistics and data mining, Pierre Mancini, said yes. He also said that you would not be statistically analyzing the reversibility of alopecia unless the adverse event was "long-standing, persisting or permanent." He agreed with that.

So they decided, Sanofi -- not the plaintiffs. We didn't make this up. Sanofi decided long before our clients ever received Taxotere that they were going to study the reversibility of this drug as it relates to alopecia -- excuse me, the reversibility of alopecia.

So when you look at *Burst v. Shell Oil* that is the unicycle that the defense is riding around today, it doesn't stand. It is a categorically different type study and easily distinguishable from what you have before Your Honor.

Now, one of the other things, a big criticism that they make, is that Dr. Madigan is not capable of providing

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testimony in this case, and they quoted you to the *Abilify* MDL decision where they said he was excluded from testifying. He was excluded, Your Honor, from giving medical testimony. Thankfully, we are not asking him to give medical testimony in this case, and there's no reason for the Court to consider it. There's no reason for an order to issue excluding his ability to offer medical opinion because he is not giving medical opinion.

If you read what Mr. Strongman quoted from, that "Dr. Madigan is a man of statistics, not medicine. He is not a medical doctor, toxicologist, pharmacologist, or psychologist. He also has no specialized knowledge of or clinical experience," and it goes on, but what they didn't put on that screen is the next two pages of this opinion that begins thusly:

"Nevertheless, the Court finds Dr. Madigan amply qualified to offer a biostatistical analysis of the evidence in this case, as well as opinions related to pharmacovigilance and clinical trials generally, as his credentials in this field are well beyond reasonable challenge."

He did exactly in the *Abilify* MDL what we are asking him to do here, a FAERS database. The *Abilify* court endorses him to do that. He does an analysis of internal pharmacovigilance databases. The *Abilify* court said Dr. Madigan is perfectly qualified to do that, to look at

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clinical trials and to do a meta-analysis. He is perfectly qualified to do that, and that's exactly what we are asking him to do here.

The challenge that is somehow offered in the selection of two witnesses for this motion -- there's motions against Dr. Feigal individually and there's motions against Dr. Madigan individually. This motion we see as a second bite at the apple, and they are asking to look at them again. Well, they have been looked at by other courts and they found it to be valid.

Now, Dr. Madigan certainly has testified in his deposition that individual case reports in and of themselves are not particularly helpful, but he does state that they point in the same direction as the randomized controlled trials that when you do a meta-analysis yields a statistically significant result. That is what a statistician does.

We have already looked at what the reference manual says on pooling studies. It's not uncommon for studies that are powered for safety -- which you want a share of safety in 20, 30, 40 percent of the people that use it -- need fewer people than to demonstrate a risk that is going to be seen in 4.2, 3.9, 6.1. There's various numbers that pop up in this case. You have to combine well-designed, well-controlled clinical trials that standing alone are not statistically significant are given the power to see the true result.

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The other criticism about case reports, Dr. Kopreski -- who we believe whose analysis needs to be excluded and doesn't need to be relied upon by other experts -- he agreed that when you see case reports in groups as small as five and six, that can be a trend. Case reports are on the lower rung of the hierarchy --

THE COURT: Right.

MR. MICELI: -- but, Your Honor, they are not to be thrown away. As an example, if I were to give you a quarter today, would you call yourself rich? No. But if I filled this room with quarters, would you be rich? Yes, you would. That's the way that adverse event reports work. That's why you do a disproportionality analysis.

Dr. Madigan explained the limitations of it, but you look at the background rate of all other drugs and how many get reported with this drug and you see the difference. He didn't do it just for Taxotere. He did it for paclitaxel or Taxol. He did it for Adriamycin. He did it for cyclophosphamide. He looked at the background rates of those other drugs, and the only one that shows a consistent disproportional rate of reporting, starting long before what the defendants may stand up later and say is stimulated reporting, has been consistent. Patients that use Taxotere disproportionately report permanent, irreversible alopecia.

Now, I've gotten off track a little bit with the

12:25 seven-minute presentation that I had planned this week coming into today, but I do want to touch on a couple of other cases that are in the defendants' brief because they cite them as if they are actually supportive of their position when I believe they are actually supportive of the plaintiffs' position for the admission of Dr. Madigan and Dr. Feigal.

The *Wells v. SmithKline Beecham* case -- it's a 2009 case out of the district court in the Western District of Texas -- in that particular case, the plaintiff offered a disproportionality analysis internal to the company to demonstrate general causation. Dr. Madigan admits that his disproportionality analysis does not prove general causation. It's just another piece of evidence that points in the same direction.

The same is true when the defendants cite to *Meade v. Parsley*. In that particular case, they cite it for the proposition that we can't rely upon company documents in order to establish general causation, which is simply nowhere in the law. What *Parsley* stands for is -- there was a plaintiff who took a drug called metoclopramide, who then had a doctor that said it might cause tardive dyskinesia --

THE COURT: Right.

MR. MICELI: -- an involuntary movement condition, and that's it. They couldn't say that it did cause it in this person; it might cause it. Then they said, "Well, if you look

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at the label, the label has tardive dyskinesia in it as a potential adverse effect so, therefore, that's how I'm going to prove my general causation."

This case is categorically different. We have covered the waterfront with a toxicologist who discussed it, Dr. Plunkett, whose oral argument was withdrawn but whose motion is still before Your Honor. We have a biostatistician that has gone through various strands of evidence.

We have Dr. Feigal, who I haven't even really addressed yet, but she goes through the same various strands of evidence but from a different perspective. When you look at her perspective -- Your Honor has met Dr. Feigal.

I know it's not Science Day. I'm not allowed to say that, am I?

Dr. Feigal is actually a very unique person in this case because she has experience in academia, she has experience in industry as an executive medical officer, and she has 12 years at the National Cancer Institute where she headed up the largest division of that portion of the Institutes of Health. She controlled over a billion dollars in clinical study funding and performed clinical studies. She did the same thing with the California Institute for Regenerative Medicine except there it was about $4 billion worth of clinical trials that she was overseeing.

She is uniquely qualified to render her opinions

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in this case. Without going into the granular detail, her report sets out and the deposition sets out and our briefing sets out the pains that she went to to go through various strands of evidence. It is precisely what other courts have criticized experts for not doing.

The toxic torts are simply inapplicable because they don't have the randomized controlled trials that we do. I can continue to talk about --

THE COURT: I don't think we need to talk about the qualifications of Dr. Madigan or Dr. Feigal.

MR. MICELI: Thank you, Your Honor. I have this one screen here and I only put it up and I'm going to hit it from about 30,000 feet, Your Honor.

They challenge methodology, lack of qualifications -- we just discussed that and I don't need to go through those -- and that the opinions are irrelevant and unreliable.

Your Honor, the difference between saying that a label says something and it says a word like "tardive dyskinesia" proves general causation and an in-depth analysis by a medical doctor internal at Sanofi that reviews the clinical trial data, the worldwide pharmacovigilance database, the medical literature, biologic plausibility evidence, and the adverse events internal to the company and then comes to the conclusion that there is reasonable evidence to establish a

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causal association -- and those are terms of art that mean general causation -- that it is reasonable evidence of a causal association between Taxotere were her words -- not TAC, Taxotere -- and permanent, irreversible alopecia, that's Sanofi's employee's position. Our experts have done their individual thorough investigation and come to the same conclusion and confirm it.

The fact that all compass points point north in this -- their investigation points to it, our investigation points to it, the research outside of Sanofi that is published, the published medical literature points to it -- tells you that north is where the needle is pointing and that's at Taxotere.

Thank you, Your Honor.

THE COURT: Short, short, short.

MR. STRONGMAN: I appreciate your indulgence, Your Honor.

I do want to start with one clarification too. Mr. Miceli indicated that the *Accutane* case was reversed. If you look at our slide, we actually cite the fact that while the intermediate court did, it was ultimately affirmed by the New Jersey Supreme Court. It is good law, and Dr. Madigan was roundly criticized in that case.

A couple of other points. Mr. Miceli used the analysis about quarters in the courtroom and if you got enough of them you would be rich. The problem with that is that it

12:32 ignores the Fifth Circuit law. Fifth Circuit law is straightforward. Again, it's cited by Judge Vance:

"Case reports, which anecdotally describe an occurrence, often on an individual basis, cannot establish general causation 'because they simply describe reported phenomena without comparison to the rate at which the phenomena occur in the general population or in a defined control group; do not isolate and exclude potentially alternative causes; and do not investigate or explain the mechanism of causation.'"

Case reports don't cut it. What we know is that at the end of the day, the TAX clinical studies were not statistically significant. Mr. Miceli doesn't dispute that. Dr. Madigan doesn't dispute that. Instead, he says he put them together and that's reliable. I challenge the plaintiffs to point to a case that says you can create statistical significance out of whole cloth by putting two statistically insignificant results together. It doesn't exist, and we cite law to the contrary in our briefs, including the *Zoloft* case.

With regard to the second bite at the apple, I want to make clear what we are doing here, why the framework of our motions exists the way it does.

THE COURT: Actually, I wondered about that myself, to be honest.

MR. STRONGMAN: When you read Dr. Madigan's report -- which I'm sure you will or have -- he is offering opinions on

12:33 safety signals. We filed a motion attacking Dr. Madigan's opinion on safety signals.

When you read Dr. Feigal's report, she is offering general oncology opinions and opinions about the informed consent process, so we filed a motion attacking her informed consent opinions.

When you read their reports, you do not see opinions about general causation. So when we went and took depositions of all of these witnesses, we asked them:

"Are you the general causation expert?"

"Are you the general causation expert?"

"No."

"No."

"No."

Dr. Kessler: "No."

The only two that said yes were Dr. Madigan and Dr. Feigal, so that's why we had to attack them in a general causation brief.

The plaintiffs, in essence, are trying to patch together something that they didn't put forward in the four corners of their report to begin with, and it's simply not enough.

Thank you.

THE COURT: Thank you.

Mr. Miceli and Mr. Strongman, can I get y'all to

12:34 come up here because I don't want to have 18 people.

(Off the record.)

THE COURT: Okay. We are going to continue the specific causation argument to the same date as we are doing the preemption argument, and that is what day? That's what I just talked to Mr. Strongman and -- those people, I think, that were arguing that will be available. I'm just a bit distracted. We will argue the specific causation on the same date as we do the preemption.

I am still going to meet with the trial team after this. I just didn't want to bring 50 people up here to have this conversation. So we are done for today except those members of liaison counsel and trial team.

Court is adjourned. We will have that argument on that date. Since we will be returning to argue preemption, we can do specific causation at that time.

THE DEPUTY CLERK: All rise.

(Proceedings adjourned.)

* * *

CERTIFICATE

I, Toni Doyle Tusa, CCR, FCRR, Official Court Reporter for the United States District Court, Eastern District of Louisiana, certify that the foregoing is a true and correct transcript, to the best of my ability and understanding, from the record of proceedings in the above-entitled matter.

/s/ Toni Doyle Tusa
Toni Doyle Tusa, CCR, FCRR
Official Court Reporter