UNITED STATES DISTRICT COURT
DISTRICT OF NEVADA
BEFORE THE HONORABLE MIRANDA DU, DISTRICT JUDGE
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AMARIN PHARMA, INC., and AMARIN PHARMACEUTICALS IRELAND LIMITED, Plaintiffs, -vs- HIKMA PHARMACEUTICALS USA INC., et al., Defendants.	No. 2:16-cv-02525-MMD-NJK January 14, 2020 Reno, Nevada Volume 2

TRANSCRIPT OF BENCH TRIAL

APPEARANCES:

FOR THE PLAINTIFFS:	MEAGAN P. KEANE, CHRISTOPHER N. SIPES, MICHAEL KENNEDY, JEFFREY ELIKAN, JOSEPH KENNEDY, ELAINA M. WHITT, BARBARA KURYS, HAN PARK, DANIEL J. FARNOLY and ERIC R. SONNENSCHEIN Attorneys at Law, Washington, D.C.
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Reported by:	Kathyrn M. French, CCR #392, RPR Official Reporter U.S. District Court Reno, Nevada

(Appearances continue on next page.)

APPEARANCES CONTINUED:

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RENO, NEVADA, TUESDAY, JANUARY 14, 2020, 8:30 A.M.

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THE COURT: Good morning. Please be seated.

All right. Counsel, did you resolve the issue with respect to Mr. Klein's demonstrative exhibits yesterday? Is there any objection to the Court attaching them as minutes to yesterday's hearing -- yesterday's trial, I mean?

MS. KEANE: Good morning, Your Honor. Meagan Keane.

Your Honor, we did have a chance to review the demonstrative. In our view, there is an error that's in the demonstrative with respect to a couple of patents that are actually listed both for the REDUCE-IT indication as well as for MARINE. So we don't think the slide is accurate as it's depicted.

What we would propose is that we are willing to work with defendants' counsel to come up with a compromise version that we can agree on and attach that as a demonstrative.

THE COURT: You're referring to DX 2699.

MS. KEANE: To the summary slide with respect to the list of patents, yes, Your Honor.

THE COURT: And that approach sounds agreeable to me. What I was asking, though, is that with the entire set

of exhibits that I admitted into evidence but that Mr. Klein had referenced during his cross-examination where he would show the exhibit and then highlight certain portions of the actual exhibit and reference DDX and then the number. That's what I was concerned about.

MR. SIPES: We apologize, Your Honor. This is Christopher Sipes.

What we thought might make sense, since demonstratives usually wouldn't be attached, would be for defendants to prepare just a chart that correlates the DDX number to the DX number and page. So it would be a simple chart, and that would make the record clear without having the argumentative parts of the demonstrative in, and we could just review that to make sure that it was accurate.

THE COURT: I think that would address my concern. All I want is to make sure that there's notation in the record as to whatever the reference is to DDX and then the specific slide number.

MR. SIPES: And the advantage of that, that would be a short compact thing that we just would provide the reference, Your Honor.

THE COURT: Mr. Klein?

MR KLEIN: Your Honor, we can put together that chart if you would like, but there was no argument in any of the demonstratives. You might be thinking of the opening

statement. But it was just call-outs.

THE COURT: I think the chart serves my purpose. All I want is to make sure that -- there were times when I thought that you didn't note the actual page of the exhibit but you noted the DDX number for certain exhibits that you were showing, that it's clear for the record which page of the actual exhibit you were referring to.

So the chart will suffice, and the chart will then be attached to yesterday's trial minutes.

MR KLEIN: Okay. Thank you.

THE COURT: All right.

And then on Exhibit 2299, I'm pretty sure that's the one that's left that I need to resolve; is that right?

THE CLERK: Yes.

THE COURT: That the parties will confer and let me know if you are able to reach a resolution.

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

THE COURT: All right. Let's proceed with Amarin's next witness.

MR. M. KENNEDY: Your Honor, this is Michael Kennedy for Amarin. Amarin calls Dr. Matthew Budoff.

THE COURT: Thank you.

MR. M. KENNEDY: Your Honor, we have some demonstratives with this witness as well as a witness binder. Permission to approach to distribute the binder, and if Your

Honor would like a copy of the slides as well.

THE COURT: I do not, but I don't want to have the same problem with reference to the page number of the slides. So if the slide is referenced as an exhibit, then you need to reference the actual page number of that exhibit.

MR. M. KENNEDY: Understood, Your Honor.

THE COURT: Thank you.

MATTHEW BUDOFF, M.D.,
called as a witness on behalf of the Government,
was sworn and testified as follows:

THE CLERK: Please be seated.

State for the record your full name and spell both your first name and your last name.

THE WITNESS: Matthew Budoff; M-a-t-t-h-e-w, B-u-d-o-f-f.

MR. M. KENNEDY: Good morning, Dr. Budoff.

THE WITNESS: Good morning.

DIRECT EXAMINATION

BY MR. M. KENNEDY:

Q Are you currently employed?

A Yes.

Q Where are you employed?

(Discussion held off the record.)

BY MR. M. KENNEDY:

Q Dr. Budoff, where are you employed?

A I'm employed at the David Geffen School of Medicine at

UCLA, formerly known as the UCLA School of Medicine, as well as the Lundquist Institute which is a research institute at my home institution.

Q **At a very high level, please describe your job responsibilities in those roles.**

A **Yes. So my primary responsibility is teaching. I am the program director for the Division of Cardiology, which means I teach all of the cardiology fellows, those people who are doing three years of advanced training in cardiology, on how to practice cardiology.**

I also have the opportunity to teach residents, medical students, and other clinicians.

And then, when I'm not teaching, I'm either doing clinical work, seeing patients directly, or doing clinical research.

Q **Were you retained as an expert by a party in this case?**

A **Yes.**

Q **Which party?**

A **Amarin.**

Q **So at a very high level what were you asked to do in this case as an expert?**

A **Yes, I was asked to opine on the patents and understand if there would be infringement in this case if a generic version of a product was brought to market.**

Q **Do you specialize in a particular area of medicine?**

A **Yes.**
Q **What area?**
A **It's called cardiovascular medicine or commonly known as cardiology.**
Q **What is cardiology?**
A **Cardiology is the practice of evaluating the heart.**
Q **Do you have a subspecialty within cardiology?**
A **Yes, I'm a preventive cardiologist.**
Q **What is a preventive cardiologist?**
A **So a preventive cardiologist works to try to prevent either the first heart attack in those patients at high risk of heart disease, or the second heart attack, what we call secondary prevention, in those patients who have already suffered a cardiovascular event.**
Q **Are there other subspecialties within cardiology that you're familiar with?**
A **Yes.**
Q **Such as?**
A **There's imaging, there's invasive cardiology, those people who spend most of their time putting in stints and bypass and other devices, and then there's general cardiology as well.**
Q **How long have you characterized yourself as specialist in preventive cardiology?**
A **About 20 years.**

Q **How long has the field of cardiology recognized preventive cardiology as a subspecialty?**

A **It's been about ten years since it was formalized as a subspecialty.**

Q **So what did you call yourself before preventive cardiology was formalized as a subspecialty?**

A **So if there was no check box that said preventive cardiologist, then I generally -- I would have to refer to myself as a general cardiologist.**

MR. M. KENNEDY: Mr. Brooks, can we have Plaintiffs' Exhibit 1161, please.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, you should have this document on your screen as well.**

A **Yes.**

Q **Do you recognize this document?**

A **Yes.**

Q **What is it?**

A **It's my curriculum vitae or CV.**

Q **What does your curriculum vitae contain in general?**

A **It goes through my education, training, my current work and prior work opportunities, and then it lists all of my manuscripts and abstracts.**

Q **Does Plaintiffs' Exhibit 1161 accurately summarize your professional and educational background?**

A **Yes.**

MR. M. KENNEDY: Your Honor, we would like to admit Plaintiffs' Exhibit 1161 into evidence.

MR KLEIN: No objection.

THE COURT: 1161 is admitted.

(Plaintiffs' Exhibit 1161 received in evidence.)

BY MR. M. KENNEDY

Q **Dr. Budoff, have you worked with us to prepare slides to aid your testimony today?**

A **Yes.**

Q **Or I should say to illustrate your testimony today?**

Have you prepared one such slide that summarizes your educational qualifications?

A **Yes.**

MR. M. KENNEDY: Mr. Brooks, if we could have PDX 2-2.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, is this that slide?**

A **Yes.**

Q **Could we focus on the last two items on this slide starting with the internship and residency in internal medicine. Could you describe what that involved.**

A **Yes. So, my internship and residency is three years of training to become an internist or a primary care physician.**

So I spent three years at Harbor UCLA Medical Center

affiliated with UCLA School of Medicine under that training.
Q What does it mean -- what does doing an internship in this context involve?
A So it's basically on-call every third or fourth night, taking care of patients in the hospital, seeing patients in clinic, just basically learning how to practice general medicine.
Q I would like to move to the cardiology fellowship at Harbor UCLA Medical Center. What it did that involve?
A So that's another three years of commitment. This is just focused on learning how to be a cardiologist, so I'm specializing in cardiovascular medicine and learning all of the aspects, including imaging and how to treat patients and how to do the invasive procedures.
Q And so am I correct that starting in 1997 or so you were a full-fledged cardiologist?
A Yes.
Q So you testified that you're a professor of medicine. What are your responsibilities in that role?
A So my primary responsibilities as a professor of medicine is to teach and do research. There's still an adage of publish or perish, so I still publish quite a bit as far as my academic career.
But I spend most of my time teaching, and I'll teach everybody from the primary care specialists, family medicine

doctors, and internal medicine doctors, the cardiology fellows, the interns and residents, and then the medical students who are also rotating through different rotations with me.

Q How long have you been teaching?

A Oh, I became a -- I started my professorship series in 1997 so I've been teaching full time since July 1997.

Q And am I correct that you teach practicing physicians?

A Yes.

Q Could you go into a little more detail about what you teach them.

A Yeah. So I spend a lot of time -- I get invited to a lot of different academic meetings, so I'll present at large scale meetings where there will be anywhere from dozens to hundreds of practicing physicians, and I will give lectures on -- usually on things related to lipids or things related to cardiovascular imaging to these different groups.

Q Do you have an understanding of why people ask you to do these lectures?

A Well, I've been told that I'm fairly clear when I lecture, and they find it educational so they invite me back. So I usually end up doing these on a regular basis.

Q Are you involved in any other physician education activities we haven't already covered?

A Well, I do a lot of publishing, and some of that is in

the form of guidelines. So I'll publish medical guidelines I'll write on behalf of different societies, different guidelines to help educate physicians in the field on how to practice cardiology or how to use certain tools in their practice.

Q What drew you to preventive cardiology?

A Yeah, so, I mean, the long-standing relationships with the patient, the ability to try to help them, enable them to prevent a catastrophic event was very rewarding for me, and I've enjoyed it in my clinical practice, so I've stayed with it over the many years since I started.

Q You mentioned you conduct research. What kind of research do you conduct?

A Yeah, so most of my research revolves around looking at the effect of different therapies on atherosclerosis, plaque build-up in the arteries, to see if drug X improves the arteries or if drug Y causes more problems in the arteries.

I also do a lot of research on clinical trials so I'll work with other investigators to perform clinical studies to see if a drug has its desired affect, be it anything from lowering the blood pressure to improving the cholesterol panel, to improving the triglycerides.

Q What is an investigator in the context of clinical trials?

A Yeah, so an investigator is the person who is principally

responsible for the local site, and the primary investigator or the principal investigator is responsible for the overall performance of the trial, everything from making sure the patients stay in the study and are appropriately treated, to ensuring their safety, and then to make sure that we capture all of the desired endpoints so that the trial can be published and hopefully advance science.

Q How long have you -- or how many times have you been a principal investigator at the national level?

A Probably around a dozen or so.

Q How many times have you been the principal investigator on a clinical trial at a local site?

A Oh, probably about a hundred times.

Q Can you give a few examples of clinical studies you've been involved in recently?

A Yes, I'm currently performing a multicenter trial that I'm the overall principal investigator on called EVAPORATE. That's actually using the product in question here, Vascepa, to look at plaque over time.

So I'm in charge of all of the sites in the trial and the overall performance of the trial, and I recently presented some of the interim data at the largest meeting of cardiology in the United States called the American Heart Association Meeting on a very large scale.

Q What do you hope to show in the EVAPORATE trial?

A **So EVAPORATE is -- the target of EVAPORATE is to demonstrate whether Vascepa reduces plaque in the coronary arteries as compared to placebo, so to see if some of its cardiovascular benefits that we've seen in the REDUCE-IT trial actually translate into plaque reduction at the coronary level.**

Q **Can you tell us how EVAPORATE is going so far?**

A **Yeah. It concludes in February. Hopefully by the end of the February we'll have our last patient, last visit.**

So hopefully we'll be -- we plan on presenting this at the European Society of Cardiology Meeting in July or August which is the largest meeting in the world of cardiologists.

Q **Why do you do so many clinical trials?**

A **Well, clinical trials have, I feel, a great purpose. We have to remember that about half of what we discover in -- at least in fields like cardiology, are based on these clinical trials.**

These clinical trials show us whether a drug works and in whom they work. So, for example, if we just go back to the REDUCE-IT trial, it affords us a great opportunity to understand that we can reduce cardiovascular events in patients who have certain clinical criteria. So participating in those studies help us treat patients better.

Q **You mentioned REDUCE-IT. Did you have a role in the**

REDUCE-IT clinical trials?
A Yeah, I was local principal investigator so I was responsible for my local site, and then I was a co-author on one of the recent papers describing the results in the United States population of REDUCE-IT.
Q So I think you mentioned earlier that you publish so that you don't perish. Have you prepared a slide that lists some of your publications?
A Yes.
MR. M. KENNEDY: Mr. Brooks, can we please have PDX 2-3.
BY MR. M. KENNEDY:
Q And are these some selected publications from your curriculum vitae, PX 11671?
A Yes.
Q Could you tell us a little bit more about number 1103. Is that the paper about REDUCE-IT that you just mentioned?
A Yes. So it's very important to understand how the U.S. population behaves in a clinical trial. Sometimes it's a little bit different than the overall clinical trials that are done with a worldwide influence.
So Dr. Bhatt and I put together this paper to look at the results of the -- of the 3,000 plus patients who were United States participants in the trial to see how they performed.

Q And if you could tell us a little bit more about 783. Is that also related to EPA?

A Yes. This was a review article. As I was preparing my research and preparing for the EVAPORATE trial to see how we wanted to perform that study and writing it up, we came across a lot of information related to the effects of both EPA and DHA on lipoproteins on lipids. So we wrote a little review article to help clarify that part of the science.

Q Who is the intended audience for these publications that you author?

A Yeah, so, generally, it depends on where we publish it. For example, the first publication that we discussed was published in *Circulation*. That's the Journal of the American Heart Association, so it generally goes out to all cardiologists in the United States and obviously has a bigger circulation than just the U.S. It goes around to cardiologists in the world. So that paper was more focused on getting the word out to cardiology.

Q So I would like to ask you a few more questions about your clinical practice. How long have you been seeing patients?

A I've been seeing patients since 1990 when I started my internship. We had what's called a continuity clinic, and I would see patients in my clinic starting in 1990, and I've continued since then.

Q **How many patients do you see in a typical month?**
A **So I see approximately 200 patients in different venues.**
Q **Are there -- do you have different -- do you have different places where you practice?**
A **Yes, and it depends on my rotations at the time. For example, right now I'm supposed to be in the intensive care unit, in the cardiac care unit. So tomorrow morning I will be rounding in the CCU and taking care of more acute patients.**

I also have a private clinic where I see my own patients. And I supervise fellows as well in the cardiology clinic where they will see a patient, and then I will go discuss the patient with them, go in and discuss the case with the patient, and see the patient as -- in a more supervisory role.

Q **Now, in your own practice how do those patients find you?**
A **Yeah, I have a pretty typical preventive cardiology practice. My practice entails getting referrals from primary care physicians.**

So a doctor may see somebody with high triglycerides, or may see somebody with very high LDL cholesterol, or a bad family history of heart disease and refer them directly to me, or I get patients directly from word of mouth. Some patients, some of my patients refer me, and their colleagues or friends or family members will come to see me as well.

Q **What are the common medical problems that patients face in your practice?**

A **Yeah. So my private practice, it's fairly focused on preventive cardiology. So, in other words, I try to take patients who are high risk and try to work with them on risk reduction. So that could be anything from diet and exercise to drug therapy, to other types of interventions to help prevent them from ever suffering a cardiovascular event.**

Q **Do you see patients with elevated triglyceride levels?**

A **Yes.**

Q **How often?**

A **Very frequently. Elevated triglyceride levels are part of a mixed dyslipidemia, so they're part of -- people come in with high cholesterol and high triglycerides, and then I also see patients with isolated high triglycerides.**

Q **Do you see patients with severe hypertriglyceridemia?**

A **Yes.**

Q **How often?**

A **So it's a less common disease. I don't have a lipid clinic, I have a general preventive cardiology clinic, but I do see patients regularly with severe hypertriglyceridemia.**

Q **Do you see patients with elevated LDL-C levels?**

A **Yes.**

Q **How often?**

A **So that's most the common disorder that I see and the**

most common disorder that I treat.

And, again, those patients with elevated LDL, or bad cholesterol, oftentimes have abnormal triglycerides as well. So we call that a mixed dyslipidemia.

Q Beyond your teaching, research, and clinical obligations, do you engage in other professional activities?

A Yes.

MR. M. KENNEDY: Mr. Brooks, could we please have slide PDX 2-4.

BY MR. M. KENNEDY:

Q And can you just briefly explain what you've depicted on this slide.

A Yeah, so these is just some of my recent memberships or, rather, affiliations with large organizations, national or international organizations, where my expertise was -- I was asked to be on the executive committee or be the chair of the steering committee for different groups.

Q Have you ever received any awards from your peers?

A Yes.

MR. M. KENNEDY: Mr. Brooks, can we please have PDX 2-5.

BY MR. M. KENNEDY:

Q Are these some of the awards that you've received that are reflected in your curriculum vitae?

A Yes.

Q Could you tell us about one of these awards that may be particularly meaningful to you.

A Yeah, the one that's bolded is, I think, the most prestigious is to be named an Endowed Chair.

That comes with some financial support because there's an endowment that supports your position, but, also, more importantly, you're recognized among your peers as being at the highest level of that field.

So this is the Endowed Chair of Preventive Cardiology that I was awarded in 2015.

MR. M. KENNEDY: Your Honor, at this time Amarin offers Dr. Budoff as an expert in the clinical treatment of patients with lipid disorders, including severe hypertriglyceridemia, and as an expert in cardiology.

MR KLEIN: No objection.

THE COURT: The request to certify Dr. Budoff in the clinical treatment of lipid disorders, including severe TG, and just preventive cardiology?

MR. M. KENNEDY: Cardiology in general.

THE COURT: Cardiology in general. That request is granted.

MR. M. KENNEDY: Thank you, Your Honor.

BY MR. M. KENNEDY:

Q So, Dr. Budoff, just to orient ourselves, I would like to go over a little bit of scientific background. I know some of

this was covered yesterday.

MR. M. KENNEDY: Mr. Brooks, if we could pull up slide PDX 2-6.

BY MR. M. KENNEDY:

Q So, Dr. Budoff, what have you shown on this slide?

A Yeah, so this is a lipoprotein. A lipoprotein -- I know Dr. Ketchum touched on this yesterday, but a lipoprotein is a kind of a way that we transport both cholesterol and triglycerides around the body.

If they are heavily containing both cholesterol and/or triglycerides, the bad lipoproteins, they're designated as apolipoprotein B, so you can see that in purple. And you can see within the content of that lipoprotein, that bad lipoprotein, that has both cholesterol in yellow and triglycerides depicted in red.

Q What are triglycerides?

A So triglycerides are basically how we store energy and how we then given energy to different organs when needed.

Q Are more triglycerides better?

A Well, up to a point. We need triglycerides, they are an energy source, but most commonly, especially in the United States, we have excess. We -- we have too many -- we eat too many calories, we store that as triglycerides, and triglycerides then build-up in the bloodstream which can cause plaque build-up, blockages in the arteries that then

subsequently cause heart attacks and death.

Q What purpose does cholesterol serve?

A Cholesterol is very important. It's a precursor for vitamins as well as for hormones, so it's a very important precursor.

But, again, in the United States we tend to run an excess of cholesterol, and that can, again, start to block up the arteries, gets converted into malignant cells that can then cause plaque buildup and heart attacks and strokes.

Q And what purpose does apolipoprotein B serve?

A So the apolipoproteins are divided into the good, those apo A, and bad lipoproteins, the ones that contain lot of cholesterol and triglyceride, are designated apo B.

So apo B -- I think of B as bad, so apo B is the bad lipoprotein that, when in excess, carries around too many triglycerides and cholesterol and can cause excess heart attacks, strokes, and death.

MR. M. KENNEDY: Mr. Brooks, can we have PDX 2-7.

BY MR. M. KENNEDY:

Q Dr. Budoff, what have you shown on this slide?

A Yeah, so this is just showing the natural -- the natural progression of what happens to the lipoproteins in our body.

When the liver first processes the food and creates these very low-density lipoproteins, they are very rich in

triglycerides. Then, via lipoprotein lipase and other enzymes, we deliver some of the triglycerides to organs.

And the lipoprotein gets smaller and denser, so it goes from very low-density to intermediate density. It's now a smaller lipoprotein, has less triglycerides and relatively more cholesterol, because the cholesterol is still there, and then further delivered to LDL cholesterol.

LDL cholesterol is what we commonly call bad cholesterol. This is a cholesterol-rich particle that is most associated with heart attacks and strokes and of great concern when we think about a patient's cardiovascular risk if they have too much LDL cholesterol.

Q Again, something we covered a little bit yesterday, but what is hypertriglyceridemia?

A So hypertriglyceridemia is simply hyper, too much, triglycerides, and then emia is in the blood. So too many triglycerides in the blood, and, again, that's what we call atherogenic. It causes atherosclerosis, and it causes cardiovascular events.

Q And what is severe hypertriglyceridemia, which I may also refert to STG?

A So severe hypertriglyceridemia is a less common disorder. It's an extreme state of hypertriglyceridemia mostly caused by genetics, so we know it as a chronic condition that is lifelong.

And when the triglycerides are very high, there are different risks as compared to when the triglycerides are only moderately elevated.

Q **Is severe hypertriglyceridemia a condition recognized in medical literature?**

A **Yes.**

Q **Could you give me example of the type of medical literature in which it's recognized?**

A **Yes, so it's been discussed in the cholesterol guidelines, guidelines that talk about lipids and how to treat lipids, for decades.**

Q **Now, you've mentioned guidelines a couple times. What are guidelines in this context?**

A **So guidelines are very simply the -- to establish the medical standard of care. So they instruct clinicians who are practicing in the field on the best practices and what they should do when encompassing a certain condition.**

Q **Do you use medical guidelines in your own practice?**

A **Yes, every day.**

Q **Do you have experience writing guidelines?**

A **Yes. I've been involved in probably around 13 or 14 guidelines, sometimes as the first author, sometimes as a member of the writing group.**

MR. M. KENNEDY: Mr. Brooks, could we have Plaintiffs' Exhibit 989.

And, Your Honor, I believe this is one the exhibits that has already been preadmitted in this case.

BY MR. M. KENNEDY:

Q **Dr. Budoff, do you recognize this document?**

A **Yes.**

Q **What is it?**

A **So this is a cholesterol guideline. We commonly refer to it as the Adult Treatment Panel III or ATP III report.**

Q **What role does the American Heart Association have in these guidelines? I see that this document has its logo on it.**

A **Yes, so this is -- this is a primary -- they are one the primary writers of the guidelines and sponsors of the guidelines. They are signed off by many organizations, but they are co-led by the American Heart Association and often the American College of Cardiology.**

Q **What role does the ATP III guideline play in medical practice?**

A **Yeah, so this was a very widely used and established guideline in the field. It really helped us -- directed physicians to be very aggressive with LDL or bad cholesterol control, and it also helped define some of the treatments and definitions of hypertriglyceridemia.**

MR. M. KENNEDY: Mr. Brooks, could we go to page 190 of this exhibit, PX 989. Also try page 33 -- yep,

there we go. If we could look at the table on the left-hand side.

BY MR. M. KENNEDY:

Q So, Dr. Budoff, what does this table show?

A So this table demonstrates the guidelines, recommendations for how we would categorize triglycerides. These are still used today and have been republished in many guidelines since 2002 when the ATP III came out.

You can see normal triglycerides is considered less than 150 milligrams per deciliter, so we are looking at concentrations of triglycerides in the blood, and these are always taken in the fasting state.

And then you can see borderline high triglycerides goes up to 199, high triglycerides are over 200 up to 499, and then very high triglycerides, which we also now call severe hypertriglyceridemia, is defined as greater than or equal to 500 milligrams per deciliter.

Q You mentioned something about the fasting state. Why is it important to test triglyceride levels in the fasting state?

A Yeah, so triglycerides can vary throughout the day and can vary based on our diet. So there are small changes from hour to hour. And if we had a fatty meal or a high carbohydrate meal, our triglycerides may go up a little bit, so there are variabilities.

So to accurately assess a patient's baseline, where

they're starting with their triglyceride, we do it in the fasting state so after I treat a patient, be it with diet and exercise, or be it with a drug, I can then follow that value in the fasting state to see what the net effect was of my treatment.

Q Are these classifications still used by clinicians today in 2020?

A Yes, these are the -- to my knowledge, the only commonly used classifications for hypertriglyceridemia.

Q Now, do you treat patients differently depending on which category of triglyceride level they fall into?

A Yes.

MR. M. KENNEDY: Mr. Brooks, could we please have PDX 2-8.

BY MR. M. KENNEDY:

Q Dr. Budoff, what does this slide depict?

A Yes, so this is based on -- you can see the ATP III are recommendations, that's the reference at the bottom or the source at the bottom.

And it basically breaks up the groups into high triglycerides, what are described here as 200 to 499, and then very high or severe hypertriglyceridemia, which is greater than 500 milligrams per deciliter at the top.

Q So a patient has a baseline fasting triglyceride level over 500, am I correct your primary concern at that point is

pancreatitis?
A Yes.
Q What is pancreatitis?
A So pancreatitis, as was described yesterday, is a severe life-threatening condition where the pancreatic enzymes -- the pancreas creates enzymes that are supposed to digest food.

If they have too many triglycerides, and the triglycerides block up the ducts, and the pancreas can't perform properly, those enzymes can leak out, dissolve the pancreas itself, that's inflammation of the pancreas, thus the term pancreatitis, and can also actually get into the abdominal cavity and cause much more problems.

Q Does the patient's LDL-C level affect their treatment?
A Yes.
Q How so?
A Well, so our first concern when the triglycerides are above 500 is pancreatitis because this is an acute, short-term life threatening illness. So pancreatitis can kill somebody fairly quickly, so we want to get the triglycerides below and maintain them below 500.

Once we've done that and brought them down from severe hypertriglyceridemia to -- to high triglycerides, 200 to 499, we can then further assess them to decide whether or not they're at cardiovascular risk.

If their LDL cholesterol is elevated, if they have

diabetes, if they have other risk factors, we would then consider further therapy such as a statin.

Q What causes severe hypertriglyceridemia?

A So hypertriglyceridemia is primarily a genetic disorder, so we're born with it. We don't have -- we don't process -- we don't have certain enzymes, or we have deficiencies in certain enzymes.

So when -- that original picture that I showed, when there's the VLDL, that VLDL, that very low-density lipoprotein, that big one, can't get brought down towards LDL cholesterol, so it stays in the bloodstream carrying too many triglyceride around the body, and that increases our risk of pancreatitis.

MR. M. KENNEDY: Mr. Brooks, could we have Plaintiffs' Exhibit 269.

BY MR. M. KENNEDY:

Q Dr. Budoff, do you recognize this document?

A Yes.

Q What is it?

A So this is another guideline by the American Heart Association published in the same journal as ATP III, *Circulation*, and this is a guideline specifically focusing on triglycerides and cardiovascular disease.

Q Is this a guideline that you've used in your own practice?

A **Yes.**
Q **Is this a document you relied on in forming your opinions in this case?**
A **Yes.**
MR. M. KENNEDY: Your Honor, I would like to enter PX 269 into evidence.
MR KLEIN: No objection.
THE COURT: 269 is admitted.
(Plaintiffs' Exhibit 269 received in evidence.)
MR. M. KENNEDY: Mr. Brooks, could we go to the table on page 12 of this document.
BY MR. M. KENNEDY:
Q **Dr. Budoff, what does this table depict?**
A **So this is demonstrating the -- as the table is titled, Causes of Very High Triglycerides That May Be Associated With Pancreatitis.**
Q **And the first category appears to say Genetic. Can you tell us a little bit more about that category.**
A **Yeah, so that's the largest and most common cause of very high triglyceride, thus it's listed first.**
They list the six most common genetic disorders -- seven most common genetic disorders here, but there are others as well that are listed in the document.
There are many genetic causes of severe hypertriglyceridemia. These are again the most common ones

that are listed in this table.

Q What's the second category on the list, Acquired Disorders of Metabolism? What does that involve?

A Yeah, so, you know, genetic causes are lifelong, we're born with them, they stay with us forever and require long-term therapy.

Acquired disorders of metabolism are short-term causes, what we call secondary causes of high triglyceride.

So, for example, one of the -- one of the things listed here is poorly controlled diabetes. So if a person with diabetes goes into a very high diabetic state where their blood sugar runs really high, the triglycerides can transiently, temporarily go high.

So we would eliminate this prior to medical therapy for high triglycerides because the cause of their high triglycerides is not genetics. The cause of their triglyceride problem is diabetes. So you treat the root cause. You would treat the diabetes and not treat the high triglycerides first.

MR. M. KENNEDY: Your Honor, I'm advised that there's a technical issue with defendants' screens. I was wondering if we might take a brief break to try to fix it, if they want to take a break.

MR KLEIN: Yes.

MR. M. KENNEDY: Okay.

THE COURT: Yes, and Miss Clerk will alert our IT staff and see if he can help. We'll take a brief recess.

(A recess was taken.)

THE COURT: Please be seated.

How did we resolve the issue of the monitors? Are the monitors working now?

THE CLERK: No.

MR KLEIN: They are not, but we are able to review it on the big screen.

THE COURT: Do you have hardcopies of the demonstratives?

MR KLEIN: We do, but the issue really is the call-outs from the hot seat person.

MR. M. KENNEDY: Your Honor, may I proceed?

THE COURT: Yes.

BY MR. M. KENNEDY:

Q **So, Dr. Budoff, let's go back to Plaintiffs' Exhibit 269, table 5 which was on the screen when we --**

THE COURT: I'm sorry, now my screen is not on.

(Discussion held off the record.)

THE COURT: Do you have an extra copy?

MR. M. KENNEDY: Of the slides, your Honor?

THE COURT: Yes.

MR. M. KENNEDY: We do.

THE COURT: Or I can my staff make a copy.

MR. M. KENNEDY: No -- although, Your Honor, I would say we are going to be going to particular portions of exhibits, and that's what we don't have hardcopies of is like exactly --

THE COURT: I have the exhibits. If you reference the exhibit number, I can pull up the exhibit number.

MR. M. KENNEDY: I can reference exactly where we are. I'll make sure to do that.

THE COURT: If we -- I'm not able to get the monitor to work over the noon break, we may need to move to the courtroom across the hall until we can get outside vendors to come in and fix the monitors, but that's going to require lot of changes.

MR. SIPES: Your Honor, we do have an extra copy available of the exhibits.

THE COURT: I have the exhibits. Thank you.

MR. M. KENNEDY: Your Honor, I'll make sure to identify precisely where we are in each exhibit.

THE COURT: Thank you.

MR. M. KENNEDY: So we're currently at Plaintiffs' Exhibit 269, table 5. Your Honor, that's in PX 269, that's page 2302.

THE COURT: 2302. If you'll give me one minute, let me pull up the exhibit. So, it's Exhibit 269.

THE CLERK: Your Honor, I'm going to try a small experiment and hopefully everything won't crash.

THE COURT: All right, 269.

MR. M. KENNEDY: Yeah, the pagination on the top left is 2302. There's also pagination associated with the exhibit number, and that's 12.

THE COURT: Thank you. You just need to give me the pagination associated with the exhibit number.

MR. M. KENNEDY: Understood, Your Honor.

THE COURT: I have it. Thank you.

BY MR. M. KENNEDY:

Q So, Dr. Budoff, we've been discussing the causes of very high triglycerides that are listed on PX 269, the guidelines.

Let's turn to the third category listed here which is Drugs (medications). How can medications cause severe hypertriglyceridemia?

A Yeah, so patients who already have a predisposition, already have high triglycerides, they're in the high triglycerides category, if they go on certain drugs, could push them up into the very high triglyceride category.

So it would be what we would say exacerbates or makes worse their underlying condition. So these are -- these are a list of the most common drugs that are associated with elevations in triglycerides.

Q And then the fourth category here it says Diet. How does

diet cause very high triglycerides?

A Yeah, so diet, very similar to drugs, can make worse an underlying disorder.

So patients who already have a problem with triglyceride metabolism, if they have too much alcohol, if they have a very bad diet, imagine somebody may be going from buffet to buffet eating too much, drinking too much, that could make worse an underlying condition.

But I just want to make it clear that if we were to do blood draws of most of the people who are eating too much and drinking too much at any given moment, very, very few of them would have severe hypertriglyceridemia.

This is not a common cause of severe hypertriglyceridemia, and, certainly, if you don't have an underlying problem, you don't get to that level. This is a very unusual state to see in clinical medicine.

Q So in your years of treating patients with lipid disorders, how often would you say that you see a patient who has very high triglycerides solely because of diet?

A Yeah, so that would be extremely rare. That would invoke -- once I corrected their diet, their triglycerides came down to 150 or below, came back down to normal, and I've never seen that happen.

I've seen patients who have gone from very high to high, so they've come down by 10 or 20 percent, but I've not

seen a three or four-fold reduction in triglycerides just by improving diet.

Q So a new patient walks into your office, has very high triglycerides, what's your first step in trying to treat them?

A Yeah, so my first step is always to assess what their current state of health is. So I would start with just simple questions about their current diet, how much alcohol they're drinking, do they exercise.

Then I would find out about some of these reversible causes of high triglycerides such as thyroid disease and diabetes.

And when I've eliminated all of those, let's say I have somebody who is already a good healthy patient, they're already eating well, then I would consider starting a lipid lowering therapy.

Q So if you've eliminated what you call reversible causes, and you've determined that the patient has very high triglycerides, what -- what's the next step?

A Right. So I counsel them on diet.

Unfortunately, most of us in clinical practice do not have dieticians associated with our practice. The healthcare system just does not support that. We just don't have the resources, and we don't get reimbursed for those visits. So I don't have a dietitian in my office.

I see the patient. I counsel them on diet and

exercise. I send them to resources to help them achieve a good diet and exercise assuming that they're already not doing something well.

And then, if they're not on a good diet and exercise, I would see them back in a few months to assess how well diet and exercise worked.

If they're already on an exceptional diet, which a lot of my patients who come to see me are already on a good diet, then I might start therapy at that time.

Q By therapy you mean medication.

A Yes.

Q What kind -- what medications have you used in your career to treat very high triglycerides?

A Yeah, so there are a few that -- that we've used commonly. Fibrates were the most commonly used historically, then Lovaza came out, and then finally now Vascepa is available.

Q So let's take these one at the time. What are fibrates?

A So fibrates are a therapy that specifically were designed to lower triglycerides so they've been around for decades. To my knowledge, all of them are now generic although there's a new one in development.

But they basically lower triglycerides dramatically. We get about a 50 percent reduction in triglycerides. So 600 will go to 300 when you institute an fibrate on average.

Q **So do fibrates have downsides?**

A **Yes. Unfortunately, the downside of fibrates is while the triglycerides come down dramatically, the bad cholesterol, the LDL cholesterol, goes up dramatically.**

So literally we get a 50 percent drop in triglycerides, and on average in that population we get a 50 percent rise in bad cholesterol. So you're basically trading one problem for another.

Q **So do you have medications available that could address the LDL-C rise?**

A **Yes.**

Q **Like what?**

A **So, at least up until 2016, if I put somebody on a fibrate, let's say, and their triglycerides came down but their LDL went up, let's say from 100 to 150, so now they're at a very high risk of having a heart attack because their bad cholesterol is high, I would then have to institute a statin to lower that LDL by 50 percent back down to a hundred.**

So I would have to use a high potency statin to counteract a side effect of fibrates, which is something that we always try to avoid in medicine, because now I'm putting them on two drugs instead of one.

Q **Can you characterize how often you describe fibrates to STG patients earlier in your career compared to now.**

A **Yeah, so earlier in my career they were the primary**

treatment of severe hypertriglyceridemia in my practice. They were widely used, and they were, again, generally -- there were generic versions of them so they were low cost, so I used them quite widely.

After 2016, the Food and Drug Administration opined that you cannot use a fibrate and a statin together.

So now I can't use fibrates in most cases of severe hypertriglyceridemia because, if I get that 50 percent rise in LDL, I then lose my primary way of reducing it.

Q **But when you do prescribe fibrates to a patient with STG, for how long did you prescribe them?**

A **So I would put them on a therapy for life, and with all of our chronic conditions, high cholesterol, high blood pressure, high triglycerides, those are chronic conditions, those are lifetime treatment.**

Q **So I think you mentioned Lovaza. What is Lovaza?**

A **Lovaza is a fish oil derivative. We heard a little bit about it yesterday. It is a mixture of EPA and DHA.**

Q **What -- does it lower triglycerides, and to what extent?**

A **Yeah. So it's another dramatic reduction of triglycerides. Triglycerides come down by 50 percent. So literally we see a 50 percent drop in triglycerides on average when we put a patient with severe hypertriglyceridemia on Lovaza therapy.**

Q **Is there anything wrong with Lovaza?**

A **Yeah, Lovaza has the exact same problem as fibrates in that the average LDL rise, bad cholesterol rise, is approximately 50 percent.**

MR. M. KENNEDY: I would like to call up PX 566, and, Your Honor --

THE COURT: I'm able to see it on my screen now.

MR. M. KENNEDY: Of, terrific.

BY MR. M. KENNEDY:

Q **So, Dr. Budoff, what is PX 566?**

A **This is the package insert for Lovaza.**

Q **Does the package insert go by other names?**

A **Yes, label or package insert or prescribing information.**

Q **Can we use those three terms interchangeably today?**

A **Yes.**

Q **Is this label for Lovaza a document you rely on in your own clinical practice?**

A **Yes.**

Q **Is this a document you relied on in forming your opinions in this case?**

A **Yes.**

MR. M. KENNEDY: Your Honor, I would like to move PX 566 into evidence.

MR KLEIN: No objection.

THE COURT: PX 566 is admitted.

(Plaintiffs' Exhibit 566 received in evidence.)

BY MR. M. KENNEDY

Q We talked about this a little bit yesterday, but can you just explain at a high level what is the purpose of a prescribing information for an FDA approved drug?

A Yes, so this informs and instructs physicians on when to use the drug, when it's indicated, how to use the drug, and then, if you choose to use the drug, what you would expect to happen both from the positive side of things, what benefits you will get, and also what side effects or warnings you might -- you might need to be careful of when using that drug.

Q Do you use prescribing information in your own clinical practice?

A Yes.

Q How do you use it?

A So when I'm new to a drug and I'm not very, very familiar with it, I always refer to the prescribing information, and I read the prescribing information to understand the context of that drug, when I should be using it, how I should be using it, and what to look for if I choose to use it.

MR. M. KENNEDY: Mr. Brooks, could we pull up table 2 of PX 566.

BY MR. M. KENNEDY:

Q Dr. Budoff, what is the function of this portion of the Lovaza label?

A **Yeah, so here you can see the randomized clinical trial. These are how we establish what we call evidence-based medicine. We basically do these randomized, placebo-controlled trials. These are the highest level of trials that can be done in clinical medicine.**

And this is the trial that demonstrated the effects of Lovaza in patients with very high triglycerides or what we call severe hypertriglyceridemia.

Q **What is Lovaza's indication?**

A **Lovaza is indicated to reduce triglycerides in the setting of severe hypertriglyceridemia.**

Q **You mentioned the term evidence-based medicine. What is evidence-based medicine?**

A **Yeah, so evidence-based medicine is basically how we look at evidence to understand what the best science is, and then we formulate them into manuscripts, those get incorporated into guidelines, and those get percolated and taught to practicing physicians.**

Q **Do practicing physicians practice evidence-based medicine?**

A **They are supposed to.**

Q **Now, looking at table 2, what's your take away from the clinical data that's shown here for Lovaza?**

A **Yeah, if you just look at the top line data, literally the triglyceride results, that's our primary thing that we're**

using it for, so that's the primary interest.

And you can see on the far right what the net effect is if I were to put somebody on Lovaza with severe hypertriglyceridemia as compared to somebody who got put on a matching placebo, and you can see a 51 percent reduction in their triglyceride levels.

Q Is there any other data here that is of particular interest to you as a cardiologist?

A Yes, I think the most important thing -- there was two things. One, if you look at the placebo category for triglycerides, you see a plus 6 percent rise in triglycerides.

And this is very common that over time, if you don't treat severe hypertriglyceridemia with a therapy, and you just use diet and exercise, you do not get a net benefit, and the triglycerides remain elevated. In this case, they went up by 7 percent.

Also, looking at the LDL-C at the bottom, what happens to the LDL cholesterol, I mentioned that it goes up by approximately 50 percent, on the far right you can see the average increase was 49.3 percent.

So LDL went up from a baseline here in Lovaza of about 90 to about 130, so they went from low risk, from a cardiac perspective, to high risk because I put them on Lovaza therapy.

Q Does that data affect your -- does that affect your

analysis in terms of whether to prescribe Lovaza to your patients?

A Yes. I mean, this is a very serious problem.

Our number one cause of death in men and women in the United States is heart attacks. So while pancreatitis is a life-threatening condition that we need to treat more acutely, heart disease is something that's more likely to claim lives.

And if I raise somebody's LDL bad cholesterol by 50 percent, I am literally doing harm and now have to figure out a way of counteracting that harm.

Q Is there anywhere else in the Lovaza label that discusses the effects Lovaza has on LDL-C of a severely hypertriglyceridemic patient?

A Yes, so it's mentioned in the table and in the text below the table. It's also mentioned in the warnings and precautions section of the label.

MR. M. KENNEDY: Mr. Brooks, could we go to the bottom of the right-hand column on table -- sorry, bottom of the right-hand column on table -- sorry, that's right. I apologize, this is the correct place.

BY MR. M. KENNEDY:

Q So, Dr. Budoff, is this the area of the Lovaza label you were just referring to?

A Yes.

Q In particular, the discussion at the bottom that begins "in some patients," is that the warning you were referring to?
A Yes. So literally here it says,

"Lovaza increased low-density lipoprotein... levels in some patients. LDL levels should be monitored periodically during Lovaza therapy."

Q Now, could you characterize how often you prescribe Lovaza to your STG patients earlier in your career compared to now.
A Yeah, so before Vascepa became available, I used this a fair amount. The -- it was increasingly being used.

Again, there was a competition between should I use a fibrate or should I use Lovaza. They both had robust reductions in triglycerides, 50 percent. They both had that adverse or negative side effect of raising LDL cholesterol.

So depending on the patient and their coverage, I would use one of these two therapies quite frequently.
Q So when you did use Lovaza, for how long would you prescribe it?
A So, again, it was always prescribed -- I always prescribed things as a one year initial prescription because that's the longest I can legally prescribe it, but my intent was always, once I deemed that they needed the Lovaza, it was for lifetime treatment.
Q Now, in the period before Vascepa was available, were

clinicians concerned about the LDL-C effects of fibrates and Lovaza?

A **Yes.**

Q **Did clinicians nonetheless prescribe fibrates and Lovaza?**

A **Yes. They were the only drugs available, basically, widely available. There is niacin as well, but niacin came with a lot of flushing, and that would usually limit its use.**

So I would say a vast majority of clinicians -- we had to get the triglycerides out of the severe range. Diet and exercise already failed by definition before we would start a therapy, so now these patients have a genetic cause, a lifetime problem, and need to be treated long-term with either Lovaza or fibrate therapy.

MR. M. KENNEDY: Sir, I would like to turn to Vascepa now. And, Mr. Brooks, could I have PX 1186 which has already been admitted into evidence.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, do you recognize this document?**

A **Yes.**

Q **What is it?**

A **This is the prescribing information or label for Vascepa as of December 2019.**

Q **Is this a document you relied on in forming your opinions in this case?**

A **Yes.**

Q **So I would like to turn to page 11 of this document, which should be table 2. I think we looked at this yesterday.**

But, Dr. Budoff, do you have an understanding of where the data in table 2 of the Vascepa label came from?

A **Yes, the MARINE study.**

Q **So before we go on, were you in the courtroom yesterday when Dr. Ketchum testified?**

A **Yes.**

Q **So I would like to turn to a question that the Court asked and have you address it, and I believe the question was how do you know that the effects shown in table 2 are attributable to Vascepa and not to diet and lifestyle improvement.**

Do you remember that question from yesterday morning?

A **Yes.**

Q **So are the effects shown in table 2 attributable to Vascepa and not diet and lifestyle?**

A **Yes. So the way that the MARINE trial was done is concordant with how the prescribing information is written that first you try and you implement diet and lifestyle, and in the MARINE trial that's how it was done.**

For six to nine weeks before they started -- got randomized, they were put on diet and lifestyle treatment, so the effect of diet and lifestyle already came into play.

Then we measured their baseline variables, and you can see the word baseline here. That's after the effect of diet and lifestyle.

So the first way we know this is not due solely to diet and lifestyle is that that has already been implemented and continued throughout the trial.

So these baseline variables are then, if they still had severe hypertriglyceridemia -- so it's very important to understand because we've eliminated all of those patients, as we are supposed to before prescribing Vascepa, we've eliminated all of those patients where diet and lifestyle fixed the problem.

In other words, I put them on diet and lifestyle if I was investigator in MARINE, their triglycerides dropped to 450, they're no longer able to get randomized in the trial because they do not have severe hypertriglyceridemia at the time of the randomization.

So the other way we know that this is not due to diet and lifestyle is that both the Vascepa group and the placebo group both are getting diet and lifestyle throughout the trial. So the effect on diet and lifestyle would be neutral because it's -- it's reflected in both groups.

And the only difference between group A, Vascepa, and group B, placebo, is the drug itself. So the effects are only from the drug and not due to the diet and lifestyle

influence.

Q So at a high level, how does the data in table 2 for Vascepa compare to the data we just looked at for Lovaza?

A Yeah, so, again, the primary reason, the indication for Vascepa is to lower triglycerides in the setting of severe hypertriglyceridemia.

So we look at the triglyceride results at the top, and at the far right you can see the difference. The net effect is minus 33 percent, so not quite as robust as Lovaza, not quite as robust as fibrates, but it does nicely reduce triglycerides by about a third.

If we look at the placebo group, and look at the percent change, it's plus ten percent. Just like we saw with the Lovaza group, Lovaza was plus seven percent, that the net effect of continuing diet and exercise once you've employed it, does not generally reduce triglycerides in most patients.

The average increase was -- there was an actual average increase over time if they were just maintained on diet and exercise. Remember, placebo is placebo plus diet and exercise. Vascepa, is Vascepa plus diet and exercise.

Q So moving to the LDL-C row, how does the LDL-C data shown here compare to the data we saw with Lovaza?

A Yeah, so the LDL-C -- and this is dramatically different than both fibrates and Lovaza. Now, instead of plus 49 percent, it's minus two percent.

The net effect of putting somebody on Vascepa is that LDL-C does not go up. So this is much different with much different cardiovascular implications for a patient because their LDL is not going up by 50 percent.

Q **So how did this clinical data affect your treatment decisions for your patients with severe hypertriglyceridemia?**

A **So now this became the preferred agent when it was available.**

Remember, there are still formulary issues. There are still cost issues because this is not generic, and Lovaza had a generic alternative at this time. But this would be a very compelling reason for clinicians to use Vascepa.

And I would argue in the setting of severe hypertriglyceridemia, the only reason to use it, because it's not as good a triglyceride lowering agent as Lovaza, so the reason you would pick a branded drug over Lovaza is going to be almost solely due to the LDL-C drop.

Q **But how do you know what other clinicians are doing in response to the Vascepa data?**

A **Well, I spend quite a bit of time lecturing. Literally this afternoon I was supposed to be lecturing to the family medicine doctors at my institution on hypertriglyceridemia and hyperlipoidemia. I had to move that lecture.**

But I literally interact with primary care doctors on a daily basis. I educate them on this, and I know what

they're doing in practice, and try to direct them to guideline evidence-based medicine of what the best practices are at this point in time because obviously that continues to change over time.

Q When you do prescribe Vascepa to your STG patients, for how long do you typically prescribe it?

A So, again, once I've already eliminated the short-term causes, I've made sure they're not a diabetes person out of control, I make sure that their thyroid disease is controlled, I've put them on good lifestyle and diet, and all of that has failed, as per the label, I then institute Vascepa, and I institute Vascepa for life, because the only people left are people with genetic abnormalities that cause permanent elevations in their triglycerides. So it's always a lifetime treatment.

Q Sir, are you familiar with the proposed labels that will accompany defendants' ANDAs in this case?

A Yes.

MR. M. KENNEDY: Mr. Brooks, could we please have Plaintiffs' Exhibit 1203 which I believe has been pre-admitted in this case.

BY MR. M. KENNEDY:

Q Dr. Budoff, do you recognize this document?

A Yes.

Q What is it?

A **So this is the package insert or label for the generic proposed alternative to Vascepa. I believe this is the Hikma version.**

MR. M. KENNEDY: Okay. Could we pull up Plaintiffs' Exhibit 1209 -- I'm sorry.

BY MR. M. KENNEDY:

Q **Dr. Budoff, did you rely on Plaintiffs' Exhibit 1203 in forming your opinions in this case?**

A **Yes.**

Q **Okay. So let me ask you about Plaintiffs' Exhibit 1209. Do you recognize this document?**

A **Yes.**

Q **What is it?**

A **So this is the label, or proposed label, for the generic alternative to Vascepa. I believe this is the Dr. Reddy's Labs' version.**

Q **Is this a document you relied on in forming your opinions in this case?**

A **Yes.**

MR. M. KENNEDY: Your Honor, we would like to admit PX 1209 into evidence.

MR KLEIN: No objection.

THE COURT: 1209 is admitted.

(Plaintiffs' Exhibit 1209 received in evidence.)

BY MR. M. KENNEDY:

Q Dr. Budoff, how do the proposed labels for Hikma's ANDA product and DRL's ANDA product compare to one another?

A They are very, very similar.

Q Are there any differences between those two labels that are material to your infringement opinions in this case?

A No. The only difference is I think one is proposing a .5 gram dose and one is not.

Q Is that difference material to any of your opinions you will be giving today?

A No.

Q How do the Hikma and DRL labels as of today compare to the Vascepa label PX 1186 that we looked at earlier?

A It is very, very similar. I think the only material difference is every time the word Vascepa appeared in the Vascepa label, the word icosapent ethyl appeared in the icosapent ethyl in these generic proposed labels.

Q Does that word substitution affect any of your infringement opinions in this case?

A No.

Q Does the Vascepa label as it exists today have the same indications as the DRL and Hikma labels as they exist today?

A The indications here are only for severe hypertriglyceridemia. They do not appear to have the REDUCE-IT indications listed in the generics, but my opinions

are based on the infringement of severe hypertriglyceridemia so the indications read word for word the same between the three labels.

Q So if I asked for your opinions today regarding the Vascepa label, PX 1186, would your opinion be the same if I had asked you about the Hikma label, PX 1203, or the DRL label, PX 1209?

A Yes.

MR. M. KENNEDY: So, Mr. Brooks, could we go back to PX 1186, the current Vascepa label.

BY MR. M. KENNEDY:

Q And let me just kind of go through some of the key portions we will be looking at today, starting with the indications and usage section.

And, generally, what's the purpose of the indications and usage section?

A You know, so this is, I think, you know, a very important part of the label.

This is where we decide whether or not my patient fits into the type of patients that are indicated. In other words, does this go along with the approved use of the drug, is my patient indicated to be on this therapy.

Q And let's go to the dosage and administration section.

At a high level, what's the purpose of the dosage and administration section in the label?

A **Yeah, so once I've established that the patient is indicated to be on the drug, I then have to read about how to initiate or prescribe the therapy. So this tells me what to do prior to initiation of Vascepa and then how to prescribe Vascepa specifically.**

MR. M. KENNEDY: Let's go, Mr. Brooks, to the warnings and precautions section which cuts across pages 2 and 3.

BY MR. M. KENNEDY:

Q **What do you get as a physician from the warnings and precautions section?**

A **So this is another very important section of the label. This warns me about things I need to be aware of, things I might need to inform my patients about when prescribing this therapy.**

MR. M. KENNEDY: Mr. Brooks, we already looked at the clinical study section which is 14, so let's go to the patient counseling information, section 17.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, what is the purpose of the patient counseling and information section?**

A **As you can see here, and this is pages 11 and 12 of this label, that it basically tells us what we should inform our patients when prescribing this therapy.**

So it gives us a list of things that we should do,

things that we should inform our patients about, things that we should advise our patients about when starting Vascepa therapy.

Q So when you talk to your STG patients, is the advice that you give them consistent with what's in section 17 of the Vascepa label?

A Yes.

MR. M. KENNEDY: Mr. Brooks, if we could go to the patient information portion.

BY MR. M. KENNEDY:

Q Now, Dr. Budoff, what is the purpose of the patient information section?

A Yeah, so this is literally a handout that you can give patients. I do sometimes, depending on the patient. But when I prescribe a new therapy, the pharmacist may give this out to the patient when they first give them a new treatment.

This is information for the patient. It's written in lay language, and it goes through a lot of the same sections, but it's all lay language on what should the patient do, how should the patient take the medicine, how should the patient store the medicine.

So it has slightly different information. It's all based on the patient's -- what the patient needs to know when starting Vascepa.

Q Now, we've looked at several sections of the Vascepa

label, PX 1186. I think you testified that the generics are not seeking the new Vascepa indication.

Aside from that, are there any differences in any of the sections we've just looked at between the Vascepa label on the one hand and the proposed Hikma and DRL labels on the other hand?

A There are no material differences that affected my opinion in this case.

Q Were you instructed about the legal standard to be used in evaluating whether a patent claim has been infringed?

A Yes.

Q Have we prepared a slide summarizing your understanding of that standard?

A Yes.

MR. M. KENNEDY: Mr. Brooks, if we could have PX 2-9.

BY MR. M. KENNEDY:

Q Dr. Budoff, does this slide, PX 2-9, represent the legal standard that you've been given?

A Yes.

Q And so what is the first step in determining infringement?

A So, that a -- what a person of ordinary skill in the art would understand or from the claims at the time of the invention.

Q **And you understand the Court's already performed step one of this analysis.**

A **Yes.**

Q **And then what's step two of the infringement analysis?**

A **So step two is to compare the claims and then determine whether, if you followed the label, would you infringe on the patent itself.**

Q **And have you been instructed about the legal standard to be used in evaluating whether a defendant is inducing infringement of a patent claim?**

A **Yes.**

MR. M. KENNEDY: Mr. Brooks, could we please have PDX 2-10.

BY MR. M. KENNEDY:

Q **I'm sorry, one more question about the previous standard. Did you apply the standard for infringement that we just looked at in forming your opinions in this case?**

A **Yes.**

Q **So let's look at PDX 2-10.**

Could you just give your understanding of induced infringement.

A **Yes. So, this is -- inducement is when the label encourages or recommends or instructs a clinician to meet the limitations or elements, each of the elements in the claim.**

Q **And from what point of view are the labels interpreted?**

A **So the labels are interpreted from a practicing clinician in the field or a person of ordinary skill in the art.**

Q **And which portions of the label do you look at in this analysis?**

A **So the label is taken in its entirety.**

Q **I would like to move on to the infringement issues in this case. Are you familiar with the patents-in-suit?**

A **Yes.**

Q **Oh, sorry one more question about PDX 2-10.**

What is your understanding of .2 here under the induced infringement standard?

A **That it would be at least some clinicians would inevitably infringe on the label if they -- if they -- if they followed the methods or if they were encouraged by the label to meet all of the elements.**

Q **Okay. Now let's move on to the patents-in-suit in this case, and I would like to start with PDX 21, which is on the list of pre-admitted exhibits.**

Dr. Budoff, do you recognize this document?

A **Yes.**

Q **What is it?**

A **This is patent '728.**

Q **And the full number being patent 8293728?**

A **Yes.**

Q **Is this a patent you relied on in forming your opinions**

in this case?
A Yes.
Q Now, again, in performing your infringement analysis, were there any relevant differences between the Vascepa label and either of the defendants' label?
A No.
Q So that being the case, if I asked you about the Vascepa label, would you have the same opinion if I had asked you about the Hikma or DRL labels?
A Yes.
Q So have you prepared a slide reproducing each element of claim 1 of the '728 patent?
A Yes.
MR. M. KENNEDY: So, Mr. Brooks, can we have PDX 2-11.
BY MR. M. KENNEDY:
Q Is this the slide I just referred to?
A Yes.
Q And there is a notation here that says stipulated. What does that mean?
A So my understanding is that the -- both sides have already agreed that this claim element would be met by the -- by the labels.
MR. M. KENNEDY: So, Your Honor, let me just note for the record the stipulated facts associated with this

particular stipulation are paragraphs 204 to 209 for Amarin's Vascepa product and label, 216 to 221 for Hikma's product and proposed label, and 228 to 234 for DRL's proposed label.

THE COURT: Thank you.

BY MR. M. KENNEDY:

Q So, Dr. Budoff, reviewing the claim elements for claim 1 of the '728 patent, do you follow the steps here when you use or when you administer Vascepa to treat patients with severe hypertriglyceridemia?

A Yes.

Q In your view, would other clinicians do the same thing?

A Yes.

Q Would somebody following the labeling of the Vascepa product follow every element of claim 1 of the '728 patent?

A Yes. The label encourages these steps to be taken and all of these elements to be met when prescribing these therapies.

Q So let's take these elements one at a time.

Have you formed an opinion concerning whether the contents of the Vascepa label encourages clinicians to prescribe Vascepa to a subject having a baseline triglyceride -- a fasting baseline triglyceride level of 500 milligrams per deciliter to about 1500 milligrams per deciliter as required by claim 1 of the '728 patent?

A Yes.

Q **What is that opinion?**

A **So the indication for these therapies is for severe hypertriglyceridemia, to lower triglycerides, so literally this is the indication, the literal indication of the drug to reduce severe -- to reduce triglycerides in a subject with severe hypertriglyceridemia, and that's greater or equal to 500 milligrams per deciliter.**

MR. M. KENNEDY: Mr. Brooks, could we have PX 1186, the indications and usage section, and I would like to look at the second bullet point.

BY MR. M. KENNEDY:

Q **Dr. Budoff, is this the indication you just referred to?**

A **Yes. Yesterday, I think they called this the MARINE indication, and this is the literally almost word for word of that first element.**

Q **And does each defendants' proposed label have the same indication?**

A **Yes.**

MR. M. KENNEDY: Could we go to the clinical study section, table 2.

BY MR. M. KENNEDY:

Q **Is there anything in the clinical study section relevant to your opinion that the first element of claim 1 of the '728 patent is met?**

A **Yes. I mean, this, again, is in patients with severe**

hypertriglyceridemia, and it demonstrates that use of the drug will reduce triglycerides here by an average of 33 percent.

Q Do you understand that the other asserted claims in this case have the same or very similar claim language to the element we just looked at concerning the 500 to 1500 milligrams per deciliter patient?

A Yes.

MR. M. KENNEDY: Mr. Brooks, could we have PX 2-12.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, what does this slide depict?

A So this basically just shows two slightly different claim languages and which claims use those specific claim languages.

Q And the opinion you just expressed with respect to the version of this element that appears in claim 1 of the '728 patent, would those opinions apply with equal force with the same or similar claim language that appears in the other asserted claims?

A Yes.

Q So let's move on to PDX 2-13, and this is the claim limitation requiring administration of the drug for a period of 12 weeks.

Have you formed any opinions concerning whether the contents of the Vascepa label encourage clinicians to prescribe Vascepa to their severely hypertriglyceridemic

patients for a period of 12 weeks as required by claim 1 of the '728 patent?
A Yes.
Q What is that opinion?
A That physicians, the average clinician practicing in the field will prescribe Vascepa for long-term therapy which will encompass a period of 12 weeks.
Q And would you have the same opinion if I'd ask you about the Hikma label, PX 1203, or the DRL label, PX 1209?
A Yes.
Q So let's go to the indications and usage section of the Vascepa label.
And, again, I would like to look at what we're calling the MARINE indication, which reads,
"As an adjunct to diet to reduce TG levels in adult patients with severe, over 500 milligrams per deciliter, hypertriglyceridemia."
Does the indications and usage by itself tell you anything or tell a clinician anything about the duration for which you should prescribe Vascepa?
A Yes.
Q What does it tell you?
A Well, clinicians in the field will know that severe hypertriglyceridemia is largely a genetic problem, a lifelong problem, and requires lifelong therapy. So when the

indication lists a chronic disease, then the treatment is long-term.

Q Is there anything in the indications and usage of the Vascepa label that tells you a maximum length of time for prescribing Vascepa?

A No, there's no limit put here as there would be if this was a short-term treatment for an acute condition.

Q Are the words adjunct to diet relevant to the length of time for which a clinician should prescribe Vascepa according to the label?

A Yes, and it's brought out again in the dosage and administration section talking about lifestyle and nutritional intake and physical activity, that it's maintaining this -- maintaining this therapy over the long run because you've already eliminated the short-term problems of a bad life style or a bad diet or too much alcohol use.

So after diet, you then -- and they still have high triglycerides, then Vascepa is indicated. So you've eliminated short-term and now you're left with only the chronic genetic patients.

Q So let's go to the dosage and administration section which is immediately below. I would like to ask you about section 2.1 prior to initiation of Vascepa. What does it mean to initiate Vascepa?

A So prior to starting or prescribing Vascepa, they give

you some steps that you should take and accomplish prior to implementing treatment.

Q Let me just back up just for a second. What does the word initiation mean in this context?

A Oh, to start the therapy or to prescribe the therapy.

Q So let's talk about the first bullet point under the words "Prior to Initiation of Vascepa." What is this first bullet point of the label telling you to do?

A So it specifically tells you to identify other causes, and we talked about the short-term or the secondary causes that can cause transient elevations in triglycerides, such as poorly controlled diabetes or low thyroid disease, and manage those as appropriate first.

And if there's still a problem where the triglycerides are still above 500 and they still have severe hypertriglyceridemia, then you can go on to the next step.

Q So you mentioned transient causes. Is that the same thing as -- I think you mentioned reversible causes earlier?

A Yes.

Q So let's say you follow the first bullet point under 2.1, you identify these other reversible causes such as diabetes, hyperthyroidism, and medications, and you manage them as appropriate, and let's say you successfully manage them. At that point would those patients get Vascepa?

A No. Just like the MARINE trial, if they don't still have

severe hypertriglyceridemia, they would never be implemented on treatment.

Q And then let's go the second bullet point under section 2.1 which reads, quote,

"Patients should engage in appropriate nutritional intake and physical activity before receiving Vascepa which should continue during treatment with Vascepa."

So what -- you've probably touched on this earlier, but what does this involve?

A So, again, this is what I talked about earlier. The way the MARINE trial was literally done, you first counsel them and get them to engage in a good diet and exercise.

If good diet and exercise fail, then you would initiate Vascepa. If good diet and exercise is successful, you don't use Vascepa. It would be off-label use to use Vascepa before implementing diet and exercise.

Q So if it's one of those patients who you can counsel them on diet and lifestyle, and that gets them under 500 and keeps them there, would that patient get prescribed Vascepa if the clinician were following the label?

A No.

Q So would -- so if you back out the patients who have what you are calling reversible causes, and you're backing out the patients who have diet and lifestyle related issues that get

them over 500, who is left?
A So left -- as we saw in that table from the scientific statement from the American Heart Association, the only category that's left is genetic causes.
Q And do those people get Vascepa if a clinician is following the labeling, the people with genetic causes?
A Yes. They have a lifetime problem, and they're going to develop pancreatitis, their risk of developing pancreatitis is high, so they would get Vascepa as encouraged by the label here in dosage and administration.
Q Would a clinician following the label prescribe Vascepa to somebody whose cause of STG was addressed by something mentioned in section 2.1 of the label?
A I'm sorry, can you repeat that?
Q Would somebody whose STG was adequately addressed by one of the issues mentioned in 2.1 of the label be prescribed Vascepa by a clinician following the label as a whole?
A No, they would be eliminated from being a candidate for Vascepa.
Q So let's turn to the clinical study section of the Vascepa label. And, Dr. Budoff, does the clinical study --
MR. M. KENNEDY: Mr. Brooks, can we have the verbiage above table 2 as well this time? Sorry.
BY MR. M. KENNEDY:
Q Dr. Budoff, does the clinical study section of the

Vascepa label tell you anything about the duration of treatment that the label is calling for, for Vascepa?

A Well, yes. I mean, the study designed specifically calls out that patients were enrolled in this study for 12 weeks.

Q Why is that meaningful?

A Well, because, in clinical practice, we -- we try to follow the prescribing information, and if the prescribing information was done at 12 weeks, then that informs the physician, that instructs the physician that you should wait 12 weeks to reassess lipids to see what the full effect of your treatment is, because my goal, when putting them on Vascepa, is to achieve the results in table 2.

In other words, I want to see a 33 percent drop on average in triglycerides. I want to see no rise in LDL cholesterol.

So those become really important, and the only way I can compare my patient to the label and what's being encouraged is to follow the instructions that are given, and the instructions here are to treat for 12 weeks.

Q Does the Vascepa label contain any clinical data concerning treatment of Vascepa for any duration other than 12 weeks, like, for example, four weeks?

A No, there's no other mention of any other duration of treatment other than 12 weeks.

Q So if you, for some reason, decided to prescribe Vascepa

for four weeks to a severe hypertriglyceridemic patient, what would the label tell you about what lipid effects you would expect to achieve?

A **So there are none listed here, so the label would not inform you at all on what to expect at four weeks.**

Q **And, again, just to -- the clinical studies data in table 2 of the Vascepa label, does the same data appear in the DRL and Hikma labels?**

A **Yes, the same exact language for 12 weeks exists.**

Q **The same data as well?**

A **Yes.**

Q **Dr. Budoff, is there any background information a clinician in this field would bring to bear when reading the Vascepa label?**

A **Yes. I mean, physicians who are treating patients with severe hypertriglyceridemia are generally either going to be primary care physicians, largely, may be endocrinology or cardiology, and they will be familiar with other therapies in the class. They're supposed to be familiar with the guidelines, and they are supposed to follow the label when prescribing these therapies.**

Q **So the clinicians who would be reading the Vascepa label, they would already know what severe hypertriglyceridemia is?**

A **Yes, I would hope so. Usually the physician who starts therapy understands the disease well enough to implement**

treatment for that disease.

MR. M. KENNEDY: Mr. Brooks, could we have PX 288.

BY MR. M. KENNEDY:

Q **Dr. Budoff, do you recognize this document?**

A **Yes.**

Q **What is it?**

A **So, this is a review article written by Dr. Karalis, he's a professor and cardiologist in Pennsylvania.**

Q **Generally what's the subject matter of this article?**

A **So this is a review of all of the clinical guidelines for how to manage hypertriglyceridemia, and in this paper he focuses more on the treatment with the 4-gram doses of omega-3 fatty acids, the high dose treatments that are available.**

Q **And the omega-3 fatty acids, that refers collectively to Vascepa and Lovaza?**

A **Yes.**

Q **Is this a document you relied on in forming your opinions in this case?**

A **Yes.**

MR. M. KENNEDY: Your Honor, Amarin moves PX 288 into evidence.

MR KLEIN: No objection.

MR. M. KENNEDY: Or seek to move 288 --

THE COURT: 288 is admitted.

(Plaintiffs' Exhibit 288 received in evidence.)

MR. M. KENNEDY: Mr. Brooks, could we go to page 309 of this article, the right-hand column, the section that starts "Patients with very high TG levels."

BY MR. M. KENNEDY:

Q And in particular, Dr. Budoff, I would like to ask you about the sentence that begins "If an individual with very high TG."

Dr. Budoff, what is this sentence telling you about what to do with somebody who falls into one of the very high TG groups?

A Yes, so this describes what we call step-wise care. So, and that's how every physician that I'm familiar with practices.

In other words, you do step one. In this case, let's say we put them on Vascepa therapy. That's step one. Then you see what happens after step one, and you decide if you're going to go to step two.

So this is describing the considerations of going to step two, "consideration should be given to adding a statin to their triglyceride-lowering therapy."

So it's not saying stop step one and start over, it's saying you've already put them on Vascepa, should I add a statin to further reduce their cardiovascular risk.

Q So this passage is talking about somebody who had very

high TGs, was put on an omega-3 fatty acid, and now they fall into a lower category of TG level?

A So now they're at lower level of TG level, but now they're at an enhanced level of cardiac risk so now my focus shifts.

I've treated -- I've successfully treated their high triglycerides. I maintain that, I continue that as outlined here, I continue the Vascepa, and now I say, oh, I've gotten you out of the risk of pancreatitis, but now you're at risk of a heart attack, I better do something else.

In this recommendation the something else, based on the 2013 cholesterol guidelines, is to add a statin to their regimen.

Q And just to be clear, Dr. Budoff, we're still talking about a patient with severe hypertriglyceridemia?

A Yes, the paragraph starts with "patients with very high triglyceride levels."

Q So --

A So that's literally the population that they're describing in this article.

Q And I --

THE COURT: Mr. Kennedy, may I interrupt for a moment?

MR. M. KENNEDY: Sure.

THE COURT: Earlier, Dr. Budoff, there was a

chart shown showing a patient with TG equal to or above 500 mg per deciliter, and then you -- I think the chart says the goal was to reduce their TG, and then the next category is between two something, 200 to 499.

THE WITNESS: Yes.

THE COURT: There's cardiovascular risk. Are you referring to that category of patient?

THE WITNESS: Yes. So now we've basically lowered their pancreatitis risk so now we now assess their cardiovascular risk.

THE COURT: Thank you.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, I would like to turn to the last passage in this section here that starts, "If the TG levels fall to a normal or borderline level," and what is this passage saying about how to treat patients who started with severe hypertriglyceridemia?

A Yeah, so this is now the scenario that the patient who had very high triglyceride, above 500, severe hypertriglyceridemia, we've implemented lifestyle changes, we've implemented Vascepa or another drug and a statin, and they say if their triglycerides fall to normal or borderline, consideration can be given to discontinue the nonstatin, triglyceride-lowering medication.

Q And what is normal or borderline?

A So that would be less than -- so normal is less than 150, borderline is less than 200.

So implementation in this scenario, when using Vascepa, as an example, if you started above 500, so let's say they're about 600, which is even less than the average in the MARINE trial, to get to 600 to less than 200 would be a 66 -- a two-thirds reduction in their -- in their triglyceride levels which would be double what we saw in the trials.

So I think this is an unlikely scenario. But if you do happen to achieve reversal of their triglycerides, and they come down to completely normal, then it says consideration can be given to stopping the triglyceride-lowering medication.

Q Now, in your own practice how often do you see that kind of magnitude of a reduction from someone who is at very high triglycerides to normal or borderline?

A Yes, I could say that -- I can say that I've never seen that in my practice.

In the EVAPORATE trial, which was a prospective randomized trial using Vascepa, no patients had a 66 percent drop in their triglycerides using Vascepa therapy.

Q Now, if you have a patient with very high triglycerides who achieves a triglyceride reduction with Vascepa short of that kind of 60 -- you know, 70 percent reduction, do you consider taking them off of Vascepa at that point?

A No. So if their triglyceride levels are still in the

high range, then I know if I stop Vascepa their triglycerides will go back up to baseline.

Remember, we've eliminated all of the short-term, all of the bad diets, all of the alcohol bingers, all of the diabetics out of control. What we're left with are the genetic patients, and if I stop the active treatment, triglycerides are going to go back up to where they started, and they're going to be back at risk of pancreatitis.

Q So the patients who we're talking about still have -- patients we're talking about who have very high triglycerides, and you're able to lower their triglycerides with lipid-lowering therapy, those patients are considered to have the condition of severe hypertriglyceridemia, correct?

A Yes, a chronic condition -- you don't take away the diagnosis once you've controlled it. If somebody has high blood pressure, and I treat them, and now their blood pressure is reading normal, I don't tell the patient, oh, you no longer have high blood pressure, the patient has high blood pressure still, they just are treated or have successfully controlled high blood pressure.

I just want to point out the last sentence of this paragraph, it says,

"Triglyceride levels will need to be monitored closely for any rise in triglycerides."

So even Dr. Karalis in their review of the

guidelines are reminding you that if you stop the therapy, you best keep an eye on them because they're likely to go back up.

Q Would you -- if you put some patient with STG on Vascepa, have you ever seen them have their triglycerides lowered before 500 in less than 12 weeks?

A No. I don't measure less than 12 weeks. That's not only a practice with Vascepa, that's a general practice with all lipid-lowering therapies.

The statins, for example, the most common practice, the advocated practice, the way the trials were done, is to put them on a new therapy. Let's say I put them on Lipitor, a statin, I would follow them up at three months.

I don't get a lipid level at four weeks or six weeks, so I would not know what happens in the short run, I want to see what happens in the long run because this is a chronic disease that's going to be needed to treat long-term.

MR. M. KENNEDY: Mr. Brooks, can we go back to PX 989 which we put into evidence earlier today.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, this is the ATP III we discussed earlier.

A Yes.

MR. M. KENNEDY: Mr. Brooks, could you please go to page 195, and there's a passage concerning very high triglycerides.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, what is this passage attempting to convey?

A So, again, this goes through -- basically these are the guidelines, but they basically go through the same steps as the label.

You start with looking for drugs that could increase triglycerides and preferentially discontinue those drugs. You eliminate alcohol. You make sure that their diabetes is under good control.

And then it starts talking about diet and lifestyle changes, and then ultimately what triglyceride-lowering therapies you could institute if all of those first steps are not successful.

Q I would like to ask you about towards the end of this passage where it says,

"For most persons with extremely high triglycerides, therapy can be considered successful if it reduces serum triglycerides below 500."

Do you see that?

A Yes.

Q What does it mean -- what does the ATP III mean by successful in this context?

A Yeah, so all chronic diseases have goals. We always have a goal when we're implementing therapy. Our blood pressure

goal is to get the blood pressure down to below 130 or even down to below 120 millimeters of mercury. Our diabetes goals are to achieve a hemoglobin A1C of 6.5.

When we achieve those goals, we're considered to be successful. That doesn't mean that we stop therapy, that just means we've achieved our goal, and now we continue therapy, we maintain therapy, to keep the patient at that goal.

This is saying the same thing about severe hypertriglyceridemia, that when you get the triglycerides below 500, you've achieved your goal, you've lowered their pancreatitis risk.

It says they're often not possible to normalize triglycerides. Going back to what Dr. Karalis talked about, you can -- most of the time you're not getting them down to 150 and can stop therapy, you're just getting them under 500, and now you maintain that drug to maintain your goal, so you maintain success over time.

Q And in this -- just to clarify, in this context extremely high triglyceride, that means severe hypertriglyceridemia?

A Yes.

Q And, again, just to clarify, somebody with severe hypertriglyceridemia who is on medication and gets below 500, those patients are still considered to have the condition severe hypertriglyceridemia?

A Yes, they have the disease, they're just being

controlled. They're controlled for -- with severe hypertriglyceridemia.

MR KLEIN: Objection real quickly. I've given counsel a lot of latitude, but there's a fair amount of leading going on.

THE COURT: I consider the last few questions summarizing what Dr. Budoff already testified, so to the extent there's an objection, that objection is overruled.

BY MR. M. KENNEDY:

Q Has FDA expressed a view on whether triglyceride-lowering medication is needed after the patient's TG levels are reduced below 500?

A I'm sorry, can you we repeat that?

Q I'm sorry. Has FDA expressed a view as to whether TG-lowering medication is needed after a severely hypertriglyceridemic patient is reduced below 500 milligrams per deciliter?

A Yes.

MR. M. KENNEDY: Let's look at PX 289 which I think is on the list of pre-admitted exhibits.

BY MR. M. KENNEDY:

Q Dr. Budoff, do you recognize this document?

A Yes.

Q What is it?

A So this was very nicely described by Dr. Ketchum

yesterday. This is the medical review, what the FDA publishes to go along with their decision with the -- with the product for, in this case, Vascepa.

Q And I would like to go to page 40 of this document. There's a heading called Efficacy Summary.

And, Dr. Budoff, does this passage have any significance to your opinion concerning the duration of treatment indicated by the Vascepa label?

A Yes. They talk about the indication, and then the second sentence is,

"Patients with very high triglycerides have a strong genetic component to their disease and have an increased risk for acute pancreatitis."

So, again, genetic implies lifelong problem, implies lifelong treatment.

Q Does FDA speak elsewhere in this document to the need to maintain TG-lowering therapy in patients with SHT?

A Yes.

MR. M. KENNEDY: Mr. Brooks, could we go to page 67.

BY MR. M. KENNEDY:

Q And directing your attention to the heading 6.1.9, does this passage from the FDA review bear on your opinion concerning the duration of treatment for SHT patients indicated by the Vascepa label?

A **Yes.**
Q **How so?**
A **So, I mean, this talks about the four-week and the additional 40 weeks, the one year data that was available as described by Dr. Ketchum yesterday, and they just say that the effect of Vascepa 4 grams occurred by week four and the effects were maintained throughout the study.**

And then the label only talks about the 12-weak data because that's the primary target of the trial and our most common practice when we follow-up patients.
Q **I think you've mentioned this earlier in your testimony, but do you prescribe other lipid-lowering medications other than TG-lowering agents?**
A **Yes.**
Q **Could you give some examples.**
A **In what context?**
Q **Like other than -- you know, anything you prescribe to your patients other than Vascepa, fibrates, or Lovaza.**
A **Yeah, now we use statins, blood pressure medications, many therapies.**
Q **Do some of those other therapies call for indefinite treatment?**
A **Yes. I mean, the label never says treat indefinitely, but the label talks about a chronic condition, and the chronic condition therefore is treated long-term.**

I think I spoke earlier to when I start a statin, I -- the intent when I put a patient on a statin is that they're going to take it for the rest of their life.

MR. M. KENNEDY: Mr. Brooks, could we have PX 277.

BY MR. M. KENNEDY:

Q Dr. Budoff, do you recognize this document?

A Yes.

Q What is it?

A This is the National Lipid Association guidelines published in 2015.

Q What is the National Lipid Association?

A So the NLA, or the National Lipid Association, is the largest body of physicians who are primarily interested in controlling lipids, so lipids being bad cholesterol, LDL predominantly, and triglycerides, as the two most common that are measured and treated.

Q Are these NLA guidelines considered authoritative in your field?

A Yes.

Q Is this a document you relied on in forming your opinions in this case?

A Yes.

MR. M. KENNEDY: Your Honor, we would like to enter PX 277.

MR KLEIN: No objection.

THE COURT: PX 277 is admitted.

(Plaintiffs' Exhibit 277 received in evidence.)

MR. M. KENNEDY: And, Mr. Brooks, could we turn to the page marked 154 at the top, and I would like to direct you to the paragraph Follow-Up Visits that cuts across two columns.

BY MR. M. KENNEDY:

Q Dr. Budoff, does this passage bear on your opinion concerning the duration of treatment indicated by the Vascepa labeling?

A Yes. I mean, this -- this starting with the word -- with the very last sentence, once goal levels have been achieved, so this just speaks to you've now achieved your goal or your target, you've been successful as we've described before.

"...response to therapy should be monitored...to confirm continued success in maintenance of goal levels and patient adherence."

In other words, you don't stop the therapy, you start monitoring them at longer intervals. You don't need to monitor them every three months anymore, but you continue to monitor them over time to make sure that they stay at goal, that you can maintain the success with your therapy, and that they remain -- the patients stay on therapy and they remain adherent.

Q **Adherent means that the patients are taking the medication as prescribed?**

A **Exactly.**

Q **When you write a prescription, do you intend that patients adhere to that prescription?**

A **Yes, I anticipate that they will follow my instructions, although we all know that not all patients are perfect in following the exact recommendations of their physician.**

Q **Now, are there drugs you encounter in your practice that do have a set limited duration of administration?**

A **Yes.**

Q **Can you think of some examples?**

A **Yes. I mean, the most common example are things like blood thinners like Lovenox or antibiotics. When we prescribe antibiotics, we give a course of antibiotics, we don't give a lifetime of antibiotics.**

MR. M. KENNEDY: So, Mr. Brooks, could we have PX 285.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, do you recognize this document?**

A **Yes.**

Q **What is it?**

A **This is the Lovenox package insert or the label for Lovenox.**

Q **And what is Lovenox used for?**

A So Lovenox is a blood thinner. It's used for acute or short-term conditions surrounding surgery or for acute clots. So we always prescribe a drug that's prescribed for acute or short-term uses for a prescribed length of time.

Q Is the Lovenox label a document you relied on in forming your opinions in this case?

A Yes.

MR. M. KENNEDY: Your Honor, we would like to enter PX 285 into evidence.

MR. KLEIN: No objection.

THE COURT: 285 is admitted.

(Plaintiffs' Exhibit 285 received in evidence.)

MR. M. KENNEDY: Mr. Brooks, could we have section 282 of the Lovenox labeling.

BY MR. M. KENNEDY:

Q So, Dr. Budoff, is this an example of a drug with a limited duration?

A Yes. So this is the dosage section of the label, and it specifically tells you the duration of administration in every single scenario.

So it gives you six different indications that Lovenox is indicated for, and in every single circumstance it talks about duration of administration because this is an acute drug that's not used long-term, so you are given this information in the dosage and usage section of the label.

Q **So I would like to talk to you a little bit about your prescribing practices for Vascepa. Is administering Vascepa for at least 12 weeks consistent with your own practice?**

A **Yes.**

Q **So when you write a new prescription to a patient with severe hypertriglyceridemia for Vascepa, when is the next time you schedule an appointment with them?**

A **Yeah, so the most common practice, the practice that I've been taught, the practice that I teach, is that you follow them up at a three-month interval.**

You get a lipid value at the end of three months which is, again, approximately 12 weeks, and then you see them a few days after their blood draw so you can review with the patient what the effect of that therapy was over the first 12 weeks of treatment.

Q **Theoretically would you find it useful if you could see them more quickly than 12 weeks?**

A **No. A lot of drugs don't hit their maximum potency or the patients may not be adherent. Remember, I'm trying to get them to stay on therapy long-term.**

So whether or not they're successful at four weeks or six weeks is totally irrelevant to the long game, and as the guidelines talk about, you need to monitor them every 4 to 12 months for lifetime to make sure that they stay on therapy.

So I'm interested more in a long-term follow-up than

an acute follow-up for my patients who have chronic diseases.
Q When you prescribe Vascepa, how much of a supply do you write the prescription for?
A Yeah, so most commonly I prescribe a 3-month supply at once. So I will give them 360 tablets, and then I will give them three refills so that will cover one year of treatment with Vascepa. That's how I implement Vascepa most commonly when I first start it for a patient.
Q Do you intend for the patients to take the entire supply as directed?
A Yes. It's always my hope that they comply or are adherent with my recommendations.
Q Do you ever tell a patient to stop taking Vascepa before the end of their supply?
A The only time I would ever stop it, and it would never be my intent to not have them take a long-term treatment for a chronic disease, but the only time I would sell them to stop it is if they had an adverse event from that therapy.

So, for example, with Vascepa, if they developed a bleeding problem, where they developed atrial fibrillation or some other problem that we know could be related to Vascepa, I might have them stop the therapy and come in and see me to make sure that they're not suffering an adverse event from taking that therapy.
Q Do you understand that the other asserted claims in this

case have the same or similar language concerning administration for at least 12 weeks?

A **Yes.**

MR. M. KENNEDY: Mr. Brooks, could we pull up PDX 2-14.

BY MR. M. KENNEDY:

Q **And are these the other variations of the 12 weeks term in the other asserted claims?**

A **Yes.**

Q **Do the opinions you've expressed today concerning the claim element for a period of 12 weeks in the '728 patent claim 1 apply with equal force to the same or similar elements in the other asserted claims in this case?**

A **Yes.**

Q **And we've generally been asking -- I've generally been asking you about the Vascepa label today. Do the opinions you've expressed concerning the 12-week claim elements apply with equal force to the Hikma and DRL proposed labels?**

A **Yes.**

MR. M. KENNEDY: So, Your Honor, I'm moving on to the next limitation. I'm happy to keep going, but I don't know if it's about time for the morning break.

THE COURT: I think we already took the morning break. I planned for us to go -- never mind. I guess it's time for our morning break.

MR. M. KENNEDY: Yeah.

THE COURT: All right. We'll take our morning break at this time.

MR. M. KENNEDY: Thank you, Your Honor.

(A recess was taken.)

THE COURT: Please be seated.

MR. M. KENNEDY: Your Honor, may I proceed?

THE COURT: Yes.

BY MR. M. KENNEDY:

Q Dr. Budoff, I actually do have one last question about the 12-weeks claim elements.

So, if you typically prescribe a multimonth or even a year supply to your patients -- strike that.

Why do you prescribe a multimonth or year-long supply of Vascepa to your patients if the clinical study in the label only has data for 12 weeks?

A Yes. So my intent is that they're going to stay on it for life. The maximum I'm allowed to prescribe, at least in the State of California, is for one year at a time so I give them a full year, and then, as I'm seeing them back, I can give them refills or give them new prescriptions after that.

Q Okay. Let's go -- Mr. Brooks, let's go PDX 2-15.

Moving on to the next claim element, the claim element requiring administration to effect a reduction in triglycerides.

Dr. Budoff, have you formed an opinion as to whether the contents in the Vascepa label encourages clinicians to administer Vascepa to effect a reduction in triglycerides as required by claim 1 of the '728 Patent?

A **Yes.**

Q **What is that opinion?**

A **That if physicians follow the label, that they will effect a reduction in triglycerides and this limitation will be met.**

Q **Have you been informed that the Court has construed the claim language "to effect"?**

A **Yes.**

Q **Have prepared a slide reciting the Court's construction?**

A **Yes.**

MR. M. KENNEDY: Mr. Brooks, let's half PDX 2-16.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, does this slide, PDX 2-16, state the Court's construction?**

A **Yes.**

Q **And what's your understanding of this construction?**

A **That it's not only the intent, but that it actually has to occur for the effect, the word effect.**

Q **And have you been informed the Court's also construed the related language "compared to"?**

A **Yes.**
Q **And have you prepared a slide reciting that construction?**
A **Yes.**
MR. M. KENNEDY: Mr. Brooks, could we please have PDX 2-17.
BY MR. M. KENNEDY:
Q **Does PDX 2-17 recite the Court's construction?**
A **Yes.**
Q **And what's your understanding of the Court's construction of "compared to"?**
A **So it just means that the change will occur -- that the change will occur and the magnitude of the change that will occur.**
Q **Did you apply the constructions of "to effect" and "compared to" in forming your opinions in this case?**
A **Yes.**
MR. M. KENNEDY: So, Mr. Brooks, let's go back to PDX 2-15.
BY MR. M. KENNEDY:
Q **And how does the claim element regarding effecting a reduction in triglycerides relate to the claim element requiring.**
"...compared to a second subject having a fasting baseline triglyceride level of 500 milligrams per deciliter to about 1500 milligrams per deciliter

who has not received the pharmaceutical composition and a concurrent lipid-altering therapy," what's your understanding of how those two elements relate to each other?

A So this is basically describing what -- the clinical trial section showing that there was a second subject, and we have a comparison in how well the Vascepa worked relative to a second subject.

MR. M. KENNEDY: So, Mr. Brooks, can we put this slide alongside the clinical study section in the Vascepa label that we've looked at today.

And, Mr. Brooks, if you could go to section 14 of the Vascepa label, and if we could get the whole --

BY MR. M. KENNEDY:

Q So, Dr. Budoff, does the clinical study section of the Vascepa label relate to your opinions concerning the "to effect a reduction in triglycerides" claim element?

A Yes.

Q How so?

A Oh, the primary results that are presented here in label two is the difference column, and the difference is comparing Vascepa 4 grams with a second subject who is not being treated, so, in this case, placebo therapy.

Q Does the clinical study section of the Vascepa label reflect a reduction in triglycerides compared to a second

subject within the meaning of claim 1 of the '728 Patent?
A Yes. That difference of 33 percent is the reduction in triglycerides compared to a second subject who is receiving placebo, which is not receiving the pharmaceutical composition.
MR. M. KENNEDY: Mr. Brooks, can we go to the indications and usage section of the label, and you might as well keep it alongside the slide.
BY MR. M. KENNEDY:
Q And, Dr. Budoff, does the second indication in the Vascepa label relate to your opinions concerning the effect of reduction in triglycerides claim element?
A Yes.
Q How so?
A So it says here as an adjunct to diet, so it's not receiving concurrent lipid-altering therapy, just receiving diet, so monotherapy in patients with severe hypertriglyceridemia. In other words, patients who are -- have triglycerides above 500 milligrams per deciliter as required in that element.
Q Do you prescribe Vascepa to your patients in accordance with the label -- with the indication?
A Largely, yes.
Q Does the clinical study section of the label inform your expectation of the lipid effects you achieve when you

prescribe Vascepa to your patients?
A Yes.
Q Why is that?
A So the -- I look towards the results that I'm expected to get with therapy, so I use the clinical trial section to say what would be my expected result, and then I see if my patient achieved that average result that was seen in the trial, and, if not, then I have to make changes in their regimen.
Q What percentage of your patients who you prescribe Vascepa experience lipid effects such as TG reduction in line with the results recited in the labeling?
A Yes, so about three quarters of patients will be at or around that number. So it's not going to be exactly minus 33.0 percent, but they will have generally about a one-third reduction.

Of the remaining 25 percent, half of those patients will have even more dramatic effects, and half of those patients will have less dramatic effects. That's just what we call the normal distribution of results when we treat enough patients.
Q When you write a prescription to a patient with severe hypertriglyceridemia for Vascepa, do you have any way of knowing whether they're going to achieve lipid effects in line with the MARINE label as opposed to being one the people who don't?

A **No, there's no good way to know in advance. That's why we repeat the lipid value at 12 weeks to see did they -- did they achieve or did they not achieve those desired results.**

Q **What lipid effects do you expect from a given SHT patient when you write the prescription?**

A **So I hope, I anticipate, I plan that they will achieve a 33 percent reduction in triglycerides and that their LDL will not go up. So, that is my goal and intent when I'm prescribing this therapy.**

I anticipate that the apo B will go down. I know we'll talk about that later. But I think that those are my goals and intent.

And then -- but some patients don't -- don't fall into that category, and they have to be -- I have to adjust my treatment based on the actual results in that individual patient.

Q **Are you aware that the other asserted claims in this case also have claim elements relating to effecting a reduction in triglycerides?**

A **Yes.**

Q **Have you prepared a slide reciting those same or similar limitations in the other asserted claims?**

A **Yes.**

MR. M. KENNEDY: Mr. Brooks, could we have PDX 2-18.

BY MR. M. KENNEDY:

Q Does PDX 2-18 recite the other claim elements relating to effecting a reduction in triglycerides?

A Yes.

Q And you also have some notations on the right-hand side concerning comparisons of various types. What does that denote?

A So those are the different languages that are used in each of the different claims.

So sometimes the language is "to effect a reduction in triglycerides compared to a second subject," we just described that, that's the placebo-controlled arm of the MARINE trial.

Sometimes it says "compared to placebo control," that's another way of saying a second subject not receiving active compound.

Sometimes it says "compared to baseline" or "in the subject," and those would imply just looking at the reductions in line with the -- per the individual and not comparing it to a second subject or a placebo control.

MR. M. KENNEDY: Mr. Brooks, can we put table 2 back up alongside this slide, and maybe blow up the table?

BY MR. M. KENNEDY:

Q So, Dr. Budoff, does table 2 of the Vascepa label reflect that administration of Vascepa effects a reduction in fasting

triglycerides of at least about ten percent in the subject?
A Yes, the average reduction is 33 percent. For compared to a second subject or placebo control, the average drop is 27 percent in the same subject or compared to baseline, and both minus 27 and minus 33 are more than a 10 percent drop.
Q And let me ask you the same question with respect to the limitation effects reduction in fasting triglycerides of at least about 20 percent compared to placebo control as required by the '560 patent claim 17.
A Yes. Both minus 27 percent and minus 33 percent are at least 20 percent, so that claim element would also be met.
Q And then, finally, does table 2 of the Vascepa label reflect that administration of Vascepa according to the label would achieve a statistically significant reduction in triglycerides in the subject as required by claim 4 of the '715 Patent?
A Yes, if you see where it says minus 33 percent, and you see the asterisk that says the P value is less than .001, so that is highly statistically significant change, so that would achieve an effect that is a statistically significant reduction in triglycerides.
MR. M. KENNEDY: Mr. Brooks, could we go to PDX 2-19.
BY MR. M. KENNEDY:
Q Now we're back on claim 1 of the '728 Patent, and I would

like to turn to the element regarding avoiding a reduction in LDL-C.

Have you formed an opinion concerning whether the Vascepa label encourages clinicians to prescribe the product described in the label to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject within the meaning of claim 1 of the '728 patent?

A Yes.

Q What is that opinion?

A That we have seen from the MARINE trial, and we have discussed already, that the LDL cholesterol does not go up, it goes down by minus 2 percent, so that is not substantially increasing LDL, that is neutral or slightly decreasing LDL.

Q And to recap, when claim 1 of the '728 refers to a comparison to a second subject, what does that comparison correspond to in table 2 of the Vascepa label?

A So that would be the placebo column. So that would be looking at the difference between the active Vascepa minus the placebo column to get the net difference which, in the MARINE trial, was minus 2 percent change in LDL cholesterol.

Q So you understand the Court's construed the language "without substantially increasing LDL-C"?

A Yes.

Q Do you have a slide showing that construction?

A Yes.

MR. M. KENNEDY: And, Mr. Brooks, can we have PDX 2-20.

BY MR. M. KENNEDY:

Q **Dr. Budoff, does this slide, PDX 2-20, recite the Court's construction of "without substantially increasing LDL-C"?**

A **Yes.**

Q **And you see the construction is "without a meaningful increase in LDL-C." What does clinically meaningful mean in this context?**

A **So clinically meaningful in clinical practice, and this was brought out yesterday as well, is a 6 percent rise. That's typically considered a meaningful increase in LDL cholesterol whereby we might have to react to it, and that makes it a clinical event that I have to then react to that 6 percent rise by changing my underlying management.**

Q **Did you apply the construction, the Court's construction of "without substantially increasing LDL-C" in forming your opinions?**

A **Yes.**

Q **And then there's the related construction that appears in different asserted claims, "without effecting a statistically significant increase in LDL-C." What's your understanding of that construction that's recited on the slide?**

A **Yes. So that, again, is -- basically, our definition of statistically significant is that it's not -- it's unlikely to**

have occurred due to chance and that it's a real change.

MR. M. KENNEDY: Mr. Brooks, can we go to the dosage and administration section of the Vascepa label.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, I would like to direct you in particular to 2.1 where it says, "assess lipid levels before initiating therapy." Do you see that?

A Yes.

Q Does this relate to whether Vascepa avoids an LDL-C increase?

A Well, yes. So, I mean, it doesn't say to address the triglyceride levels, or assess triglyceride levels before initiating therapy, it says lipid levels, and that tells the clinician to get a full lipid panel, and a full lipid panel includes LDL cholesterol as well as triglycerides.

So it's reminding the physician to get the full panel so that you can see what the effect is, not only on triglycerides, but also on LDL cholesterol.

Q Do clinicians treating STG patients typically get these lipid panels?

A Yes. It's very standard to get a standard lipid panel in all of your patients. I don't know how you would prescribe any cholesterol-lowering medicine without assessing a lipid panel before initiating therapies.

So I think this is fairly standard language for any

drug in this general class of lipid metabolism.

MR. M. KENNEDY: So, Mr. Brooks, can we pull up PDX 2-19 and put it alongside table 2.

BY MR. M. KENNEDY:

Q And is there anything in the clinical study section of the Vascepa label that speaks to whether the label encourages administration of Vascepa to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject?

A Yes, so in the LDL-C column on the far right is compared to a second subject or compared to placebo control, and that's minus two percent.

So you can see LDL-C went down by 2 percent, which is not a substantial increase or meaningful increase because it's a decrease.

Q And the second -- the -- where, in the clinical study section, does it reflect a comparison to a second subject in the way required by claim 1 of the '728 Patent?

A I mean, literally, right under the table there it says difference, and it says the median of Vascepa minus placebo. So it literally defines that it's comparing it to the second subject.

It also says it in the last sentence of the paragraph, the reduction in triglycerides observed with Vascepa was not associated with elevations in LDL-C levels

relative to placebo.
Q Why is that relevant?
A Well, they're calling that out to the clinician. This is an emphasis to the clinician that this is an important finding, and thus it's put in the table -- it's put in the text below the table to further emphasize that result.
Q Do the effects on LDL-C shown in table 2 influence your treatment decisions for SH -- STG patients?
A Yes, I think as we talked about before, the other agents in the class that are indicated to reduce severe hypertriglyceridemia, niacin, fibrates, and Lovaza, are all associated with significant increases in LDL cholesterol.
This drug is not associated with elevations in LDL cholesterol making it a unique opportunity to treat patients for their triglycerides without increasing their cardiac risk of having a heart attack downstream.
Q So let me ask a slightly broader question not limited to LDL-C effects, but also for the other lipid effects shown in table 2.
Do they -- the clinical data on table 2 influence clinicians' treatment decisions for their severely hypertriglyceridemic patients?
A Yes.
Q How -- why is that?
A So, again, triglycerides go down significantly, LDL does

not go up.

And what we haven't yet talked about, but I think is also important, is that apo B -- remember apolipoprotein B is the bad lipoprotein, actually goes down significantly.

So it has three affects that are all deemed positive for our patients with severe hypertriglyceridemia.

MR. M. KENNEDY: Mr. Brooks, can we go to the warnings and precautions section of the Vascepa label.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, is there anything in the warnings and precautions section of the Vascepa label that is relevant to your opinion that the label encourages administration to effect a reduction in triglycerides without substantially raising LDL-C?

A Yes.

Q What about this section supports that opinion?

A So, in all the other therapies, the fibrates, Lovaza, there is a warning about LDL rise in the warnings and precautions sections of those labels.

Here there is no such warning, and a doctor who is treating severe hypertriglyceridemia would know that. This would be a common knowledge of the effects of the other agents and the warnings that go with the other agents, and so the absence of that warning is important for physicians to understand.

Q **Do you understand that the other asserted -- some of the other asserted claims in this case have limitations drawn to avoiding LDL-C effects?**

A **Yes.**

MR. M. KENNEDY: Mr. Brooks, could we have PDX 2-21.

BY MR. M. KENNEDY:

Q **Dr. Budoff, does this slide depict the other claim elements and other asserted claims regarding LDL-C effects?**

A **Yes.**

Q **And, again, the different claims have different comparators such as second subject, placebo control, and baseline?**

A **Yes.**

Q **Do the opinions you've expressed today concerning the claim element, "without substantially increasing LDL-C" in claim 1 of the '728 Patent, apply with equal force to the same or similar terms in the other asserted claims?**

A **Yes.**

Q **For example, does -- does the Vascepa label reflect avoidance of a statistically significant increase in LDL-C in the subject as required by '715 patent, claim 14 patent?**

A **Yes, there was a decrease in LDL-C so there was not a statistically significant increase by definition.**

Q **So does that entail that the terms about avoiding an**

increase this LDL-C in claims 4 and 17 of the '560 patent are also met?

A Yes. Again, a decrease is without an increase by definition. So I think that those claims are all met by the results of the clinical trials section that's put forth in all of the labels.

MR. M. KENNEDY: Could we go to the slide PDX 2-22.

BY MR. M. KENNEDY:

Q Dr. Budoff, do you have an opinion as to whether the Vascepa label encourages physicians to prescribe Vascepa to severely hypertriglyceridemic patients who are not receiving a concurrent lipid-altering therapy as required by claim 1 of the '728 Patent?

A Yes.

Q What is that opinion?

A That the majority of patients treated in the MARINE trial and the indication itself both advocate for monotherapy. Monotherapy by definition is without receiving concurrent lipid-altering therapy.

Q Do you understand that the Court previously construed the phrase "concurrent lipid-altering therapy"?

A Yes.

MR. M. KENNEDY: Mr. Brooks, could we have PDX 2-23.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, is this the Court's construction?

A Yes.

Q Did you apply the Court's construction of "concurrent lipid-altering therapy" in forming your opinions in this case?

A Yes.

MR. M. KENNEDY: Mr. Brooks, can we go to trial Exhibit 1186, the Vascepa label, the indications and usage section.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, is there anything about the indications and usage that is relevant to your opinion that the label encourages administration to severely hypertriglyceridemic patients who aren't receiving concurrent lipid-altering therapy?

A Yes.

Q What -- what about the indications and usage section supports your opinion?

A So you can see the MARINE indication literally says as an adjunct to diet to reduce triglyceride levels. So diet is not considered concurrent lipid-altering therapy. The Court construed that that's a medication.

So this is literally advocating for Vascepa to be used as monotherapy without concurrent -- it's not requiring concurrent lipid-altering therapy.

Q **Do you -- so with respect to your severe hypertriglyceridemic patients, do you sometimes prescribe concurrent lipid-altering therapy and sometimes not?**

A **Yes.**

Q **Could you describe the type of patient who has severe hypertriglyceridemia to whom you would prescribe Vascepa as a monotherapy?**

A **Yeah. So a very common scenario is -- and triglycerides tend to affect women more than men, hypertriglyceridemia.**

So a very common scenario would be a young, otherwise healthy woman gets referred to me because their triglycerides are very high.

When I meet her, I ask her questions about her diet and exercise. She's already adhering to a good diet, she's already exercising regularly. I can see that she's not very overweight so I know she's an over -- overwhelmingly healthy person.

I check for diabetes and thyroid disease, and if she doesn't have any of those things, then my primary therapy is going to be Vascepa. She's on it, it's an adjunct to diet and exercise.

Now I'm going to prescribe Vascepa monotherapy. After I prescribe monotherapy, I'll see her back, and I'll assess her lipid profile in three months.

But a lot of these young, healthy people only have

triglyceride abnormalities. Her LDL cholesterol could be nice and low, and if her LDL cholesterol is nice and low, and she's otherwise healthy, then she doesn't qualify for concurrent lipid-altering therapy. I don't need to put her on a statin, she wouldn't benefit from such therapy, and I would just continue Vascepa monotherapy in that patient.

Q Is there anything about the Vascepa labeling that gives you comfort that Vascepa would be appropriate as a monotherapy in the patient you just described?

A Yes.

Q What -- what part of the label?

A So the clinical trial section also speaks to the utility of this therapy as monotherapy.

Q Could you describe the type of severely hypertriglyceridemic patient that you might prescribe Vascepa along with a concurrent lipid-altering therapy?

A Yes. So take another patient walks into my office, this time they have underlying heart disease so they might have already suffered a heart attack or maybe have a stint. Their triglycerides are over 500.

I implement diet and exercise, have them come back. They're still above 500. I now need to use Vascepa therapy in that person.

They might already be on a statin, so that would be concurrent lipid-altering therapy or, after I put them on

Vascepa and see that their LDL, their bad cholesterol, is still too high, I would then implement statin therapy.

We discussed the guidelines advocate for that step-wise care that is so important when we assess patients with high triglycerides.

MR. M. KENNEDY: Mr. Brooks, could we go to table 2.

BY MR. M. KENNEDY:

Q So is there anything about the labeling that encourages you as a clinician to administer Vascepa -- I'll start -- I'll just start without concurrent lipid-altering therapy, the young woman, for example.

A Yes. Mr. Brooks, could you expand it to the top paragraph real quickly? Sorry.

So this is the full clinical trial section, and you can see there's a sentence fairly far down in the first paragraph starting with 25 percent of patients were on concomitant statin therapy.

So that literally tells you that this -- this trial, one fourth of the patients were on a statin plus Vascepa, or statin plus placebo, and 75 percent were not.

So the vast majority of the patient results in table 2 reflects Vascepa monotherapy. That literally reflects 75 percent of the results of the patients randomized in this trial.

So the study definitely encourages physicians to prescribe Vascepa as monotherapy, and because 25 percent of patients were on statin, concomitant statin therapy, it also encourages patients to use it with concurrent lipid-altering therapy when appropriate.

Q I'd like to look at the verbiage underneath table 2. Is there anything about that portion of the clinical study section that encourages clinicians to administer Vascepa without concurrent lipid-altering therapy?

A Well, again, so two-thirds, three-quarters of the patients achieve these results without statin therapy. So this largely reflects Vascepa reduced triglycerides with without elevating LDL-C, that largely reflects the placebo, the statin -- I mean, the Vascepa monotherapy arm rather than patients who are on concomitant therapy.

Q Do you understand that some the other asserted claims have the same or similar claim language concerning administering Vascepa to STG patients without concurrent lipid-altering therapy?

A Yes.

MR. M. KENNEDY: Let's look at PDX 2-24.

BY MR. M. KENNEDY:

Q Dr. Budoff, does this slide, PDX 2-24, recite the other similar claim language?

A Yes.

Q **Do the opinions you've expressed today concerning the claim language "who does not receive concurrent lipid-altering therapy" in claim 1 of the '728 Patent apply with equal force to the same or similar claim elements in the other asserted claims that have these limitations?**

A **Yes.**

Q **And, again, the opinions -- when you've answered questions about the Vascepa label, do your opinions concerning the concurrent lipid-altering therapy claim elements apply with equal force to the Hikma and DRL labels?**

A **Yes.**

MR. M. KENNEDY: So, Mr. Brooks, can we go to PDX 2-26.

BY MR. M. KENNEDY:

Q **And I would like to do the last two elements of this patent together. These require administering orally to the subject about 4 grams per-day of a pharmaceutical composition.**

Have you formed any opinions concerning whether the Vascepa label encourages clinicians to administer orally to the subject about 4 grams per day of a pharmaceutical composition as required in claim 1 of the '728 Patent?

A **Yes.**

Q **What is that opinion?**

A **Multiple times throughout the patent physicians are encouraged to administer this medicine. The only way it can**

be administered is orally, and the only dose is 4 grams per day, so these two are automatically met by using the prescription the way it has to be prescribed.

Q So I think in your last answer you said the patent requires, did you mean the prescribing --

A The label requires.

Q So do you understand the Court previously construed the orally -- the "administering orally" claim language?

A Yes.

MR. M. KENNEDY: And, Mr. Brooks, can we go to PDX 2-27.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, is this the construction you applied in forming your opinions?

A Yes.

Q And so what's your understanding of the Court's construction of "orally administered" or "administering"?

A That the doctor is the one prescribing the medicine, and the medication is being taken by the patient at the doctor's direction. So this is a doctor-directed oral administration.

Q So writing the prescription constitutes administering?

A Yes.

Q And do you understand the parties also reached an agreement about the construction the claim term "pharmaceutical composition"?

A **Yes.**

MR. M. KENNEDY: And, Mr. Brooks, can we have 2-30.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, do you see the stipulated construction of "pharmaceutical composition"?**

A **Yes.**

Q **Is this the construction you applied in forming your opinions?**

A **Yes.**

MR. M. KENNEDY: Mr. Brooks, could we go back to slide 2-26 and put it alongside the description section of the prescribing information, section 11.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, I don't think we've seen this section of the labeling today. In general, what's the purpose of the description section of a label?**

A **This describes the medication so that the physician knows and the patient knows what it's going to look like and how -- what it constitutes.**

Q **And do the Hikma and DRL labels contain identical descriptions?**

A **Yes.**

Q **Except they're not called Vascepa, they're called icosapent ethyl.**

A **Yes.**
Q **So what in the description section informs your opinion that the label encourages administration orally to the subject about 4 grams per-day of a pharmaceutical composition?**
A **Well, the description says it's for oral use.**
Q **And what does it say about 4 grams?**
A **I don't think it says 4 grams here. I think in the dosage and administration section it speaks to 4 grams as the dose that's to be given.**

MR. M. KENNEDY: So let's go to the dosage and administration section.

BY MR. M. KENNEDY:

Q **And what about the dosage and administration section of the Vascepa label informs your opinion that the label encourages administering about 4 grams per day of a pharmaceutical composition?**
A **Under 2.2, dosage and administration, the daily dose of Vascepa is 4 grams per day, and then advise patients to swallow whole and take it with food.**

Both of those imply -- the only way you can swallow it or take it with food is an oral administration. So this covers both oral and 4 grams.
Q **And what does the dosage and administration section say about the dosage form in which Vascepa is delivered?**
A **So it's a capsule, so, again, given orally.**

Q **And are you aware that other claims at issue in this case have language similar to about 4 grams per day that appears in claim 1 of the '728 Patent?**

A **Yes.**

MR. M. KENNEDY: And can we go to slide two-dash, PDX 2-31? PDX 2-31? Oh, sorry.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, do the opinions you've expressed today concerning the about 4 grams per day claim element in claim 1 of the '728 Patent apply with equal force to the same or similar claim elements in the other asserted claims?**

A **Yes.**

MR. M. KENNEDY: And then, Mr. Brooks, if we could go to PDX 2-28.

BY MR. M. KENNEDY:

Q **And do you understand that other claims at issue in this case have the same or similar language concerning administering orally to the subject?**

A **Yes.**

Q **And do the opinions you've expressed today concerning whether the Vascepa label encourages administering orally to the subject as required of claim 1 of the '728 Patent apply with equal force to the other asserted claims with the same or similar claim language?**

A **Yes.**

MR. M. KENNEDY: So, Mr. Brooks, can we go to PDX 2-32. And you can take down the label for right now. Thank you.

BY MR. M. KENNEDY:

Q **And just so sum up, Dr. Budoff, what is your opinion concerning whether the Vascepa label taken as a whole will encourage clinicians to admit to follow each step in the method claimed by claim 1 of the '728 Patent?**

A **Yes. So as I've just outlined, every element will be met, every limitation will be met, if physicians follow the label, they will be encouraged to do all of these steps that are listed here on the slide.**

Q **In your opinion, would physicians follow the label?**

A **Yes, physicians are supposed to follow the label.**

Q **And, again, if I had asked you about the Hikma or DRL label instead of the Vascepa label, would your opinions be the same?**

A **Yes.**

MR. M. KENNEDY: So let's move on to claim 16 of the '728 Patent, and that's PDX 2-33.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, what are you depicting on this slide?**

A **So this is just the other claim that's -- that's being contested, and it just shows that all the claim elements are met in claim 1.**

So that refers to the previous slide that we just went through, all the limitations are already met, and then it describes another -- the pharmaceutical composition again which has already been stipulated or agreed upon by the parties. So all the elements for claim 16 of the '728 Patent are met.

Q So just to sum up, would the labeling -- Vascepa labeling encouraging -- encourage clinicians to follow each step of the method claimed by claim 16 of the '728 Patent?

A Yes. For all the reasons I've previously stated, physicians will -- following the label will meet all of these elements.

Q And you would have the same opinion with respect to the Hikma and DRL labels?

A Yes.

MR. M. KENNEDY: So let's move on to trial Exhibit 26.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, do you recognize that document?

A Yes.

Q What is it?

A This is the '652 Patent.

Q And so that's U.S. patent 8,367,652?

A Yes.

Q Is this one of the patents you've analyzed in forming

your opinions in this case?
A Yes.
MR. M. KENNEDY: Your Honor, I believe PX 26 is on the pre-admitted exhibit list.
THE CLERK: It is.
THE COURT: Thank you.
BY MR. M. KENNEDY:
Q And you understand that Amarin is asserting infringement of claim 1 of the '652 Patent?
A Yes.
MR. M. KENNEDY: So, Mr. Brooks, let's just go to PDX 2-34.
BY MR. M. KENNEDY:
Q And, Dr. Budoff, what are you attempting to state here where you have the notation "See Claim 1 ('728 Patent)"?
A So these are the same or similar languages that we've already discussed and demonstrated, that a physician following the label will meet all of these limitations. So the same analysis that I applied to claim 1 of the '728 Patent applies to claim 1 of the '652 Patent.
Q Now, there's one element that's not filled in here, "compared to baseline." Do you see that?
A Yes.
Q Have you formed any opinions concerning whether the Vascepa label encourages clinicians to prescribe Vascepa to a

subject to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline as required by claim 1 of the '652 Patent?

A Yes.

Q And what is that opinion?

A That they would be encouraged to lower triglycerides, and LDL will not go up when you compare that person to their own baseline, and that was done in the clinical studies section of the labels.

MR. M. KENNEDY: And let's just very quickly put this slide alongside table 2 of the Vascepa label.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, if you could just point out, does the MARINE data stated in the Vascepa label contain a comparison to baseline?

A Yes. So in the table 2, can you see under Vascepa it says the word baseline. These are the changes that are seen compared to baseline.

So to effect a reduction in triglycerides, the change was 27 percent compared to baseline. Two, without increasing LDL-C, there was a minus five percent, there was decrease in LDL-C compared to baseline. So these elements will be met when physicians follow the label.

Q And when you administer Vascepa to a subject, what kinds of lipid effects do you expect to see in that patient? I

should say a subject with severe hypertriglyceridemia.
A Right. So, again, our intent is, in our vast majority of patients, that our patients will behave similarly to the clinical trial, and these are the types of results that we will see.
So we will see a significant reduction in triglycerides with a small decrease or no change in LDL-C.
Q So, in your opinion, will the Vascepa labeling encourage clinicians to follow each step in the method claimed in claim 1 of the '652 Patent?
A Yes.
MR. M. KENNEDY: So let's move on to Plaintiffs' Exhibit 25?
BY MR. M. KENNEDY:
Q And, Dr. Budoff, do you recognize this document?
A Yes, this is U.S. patent 8,357,677.
Q Is this one of the patents you've analyzed in this case?
A Yes.
Q And have you been informed that Amarin is asserting infringement of claims 1 and 8 of the '677 Patent?
A Yes.
MR. M. KENNEDY: Mr. Brooks, can we please go to slide PDX 2-36.
BY MR. M. KENNEDY:
Q And, Dr. Budoff, again, can you just very briefly explain

what this slide shows.

A Yes. So for all the analyses that we've already described for each of these claim elements, these are the same or similar language to claim 1 of the '728 Patent, that these elements will be met in claim 1 of the '677 Patent.

The only claim -- or, excuse me, the only element that's not yet met in this is "compared to placebo control."

Q And have you formed any opinions concerning whether the Vascepa label encourages clinicians to prescribe Vascepa to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control as required by claim 1 of the '677 Patent?

A Yes.

Q What is that opinion?

A So as we've talked about before, probably now a few times, the net effect of following these elements or following the label and prescribing Vascepa the way that the label encourages, will effect a reduction in triglycerides on average by 33 percent compared to placebo control, and will lower LDL-C by 2 percent, so not without substantially increasing LDL-C compared to placebo control.

So this element will also be met based on the data in table 2 and in the paragraphs below, the paragraph below table 2, which re-emphasizes all of those findings.

Q So just to be clear, the data you just recited is from

table 2 in the clinical study section of the Vascepa label that we've looked at a couple times today?
A Yes, and then two sentences below the table that reemphasized these exact findings.
Q Do you prescribe Vascepa with the intent to achieve in your STG patient the effects recited in claim 1 of the '677 patent?
A Yes.
Q To the best of your knowledge, do other clinicians prescribe with the attempt to achieve those lipid effects?
A Yes.
Q Do patients that you treat actually exhibit lipid effects in line with what's recited in table 2?
A Yes.
Q And with what's recited in claim 1 of the '677 Patent?
A Yes.
Q In your opinion, will the labeling encourage clinicians to follow each step in the method claimed in claim 1 of the '652 patent?
A Of the '677 Patent?
Q That's what I meant, yes, I'm sorry.
A Yes.
MR. M. KENNEDY: So, Mr. Brooks, let's go to PDX 2-38.

BY MR. M. KENNEDY:

Q And this is the other asserted claim of the '677 Patent, and what are you attempting to show in the notation "(See Claim 1)"?

A So, again, based on all of the previous descriptions that we've already given and the elements that we've already addressed, that those elements will be met by the previous claim 1 of the '677 Patent.

Q Have you formed any opinions concerning whether the Vascepa label encourages clinicians to prescribe Vascepa to a subject to effect a reduction in apolipoprotein B compared to placebo control as required by claim 8 of the '677 patent?

A Yes.

Q What is that opinion?

A That physicians who are reading the label will be encouraged to reduce apo B. It occurred in the clinical trial section, it's reemphasized in the paragraph below the clinical trial section, that compared to placebo control, Vascepa will effect a reduction in apolipoprotein B.

Q What was the magnitude of the reduction compared to placebo control in apo B recited in the label?

A Minus 9 percent, and that was statistically significant.

Q Dr. Budoff, do clinicians prescribe Vascepa with the intent to achieve the apo B reductions compared to placebo control reflected in claim 8 of the '677 Patent?

A **Yes.**
Q **In your experience, does the data show that patients experience those effects?**
A **Yes, and we have ample experience that this occurs in clinical practice.**
Q **So will the labeling -- the Vascepa labeling encourage clinicians to follow each step claimed in claim 8 of the '677 Patent?**
A **Yes.**
MR. M. KENNEDY: Let's go to PX 22.
BY MR. M. KENNEDY:
Q **Dr. Budoff, do you recognize that document?**
A **Yes, it is U.S. patent 8,318,715.**
Q **Is this one of the patents you've analyzed in this case?**
A **Yes.**
MR. M. KENNEDY: And this is on the pre-admitted exhibit list?
THE COURT: Yes. It's Exhibit 40?
MR. M. KENNEDY: Twenty-two.
THE COURT: Is this the '715 patent?
MR. M. KENNEDY: Yeah, I have PX 22.
THE COURT: On the stipulated exhibit list -- oh, sorry, I'm looking at the file history. You're incorrect.
BY MR. M. KENNEDY:
Q **Do you understand that Amarin is asserting claim 14 from**

the '715 Patent?
A Yes.
MR. M. KENNEDY: And, Mr. Brooks, let's have PDX 2-40.
BY MR. M. KENNEDY:
Q And could you just describe what the notations on the right-hand side mean of this slide, PDX 2-40?
A And, again, for the same reasons that we've already discussed, the language is exactly the same or similar to those elements that we've already discussed in the claim 1 of the '728 Patent, so for the same reasons the elements will be met for claim 14 of the '715 patent.
Q Have you formed any opinions concerning whether the Vascepa label encourages clinicians prescribe Vascepa to effect a statistically significant reduction in triglycerides and apo B without effecting a statistically significant increase of LDL-C in the subject as required by claim 14 of the '715 patent?
A Yes.
Q And what is that opinion?
A That based on a lot of the discussion we've already had, that they will be encouraged to have these effects occur when they use -- when they follow the label for Vascepa or its generic proposed alternatives.
Q And, Dr. Budoff, do you understand the Court has

previously construed the term "without it effecting a statistically significant increase in LDL-C"?

A Yes.

MR. M. KENNEDY: And I think we've touched on this before, but, Mr. Brooks, if you could quickly pull up PDX 2-20.

BY MR. M. KENNEDY:

Q And directing you to the bottom claim term and construction, is this the construction of "without affecting a statistically significant increase in LDL-C" that you applied in forming your opinions?

A Yes.

MR. M. KENNEDY: Mr. Brooks if you could pull up PDX 2-40 again and put it alongside trial Exhibit 1186, page 2, the dosage and administration section.

BY MR. M. KENNEDY:

Q And directing your attention to 2.1, where the label instructs to assess lipid levels before initiating therapy, is this relevant to your opinions concerning the claim elements in claim 14 of the '715 Patent?

A Yes.

Q How so?

A We've already discussed this, but, again, it's not just telling you to assess triglyceride levels, it's telling you to assess the lipid panel before initiating therapy because

changes may occur in the lipid panel.
Q And if we could go to the clinical study section, and I -- you know, obviously we've looked at this a few times, but let me start with the claim language in this claim "in the subject."
Where in the clinical study section does the Vascepa label address levels in the subject?
A Again, that's in the baseline category that we discussed earlier under the word Vascepa.
Q And does the clinical study section reflect a statistically significant reduction in TGs and apo B compared to baseline?
A Yes.
Q How do you know it's a statistically significant reduction?
A The P values are listed there. You see the asterisks. P value for a single asterisk, which is the minus 33 percent for triglycerides, the P value is minus .001, and for the apo B, the double asterisk, minus 9 percent reflects a P value of .05. Both of those are considered statistically significant.
Q And does the clinical study section disclose an increase, statistically significant or otherwise, in LDL-C levels of the subject, or in the subject?
A No, LDL-C goes down by 2 percent or by 5 percent from baseline. Both of those are decreases. So a decrease is not

a statistically significant increase by definition.
Q And, to the best of your knowledge, do clinicians prescribe Vascepa with the intent to achieve the lipid effects and avoidance of the lipid effects recited in claim 14 of the '715 patent?
A Yes.
Q In your own experience, do your severely hypertriglyceridemic patients actually achieve effects of the type recited in claim 14 of the '715 patent?
A Yes.
Q And what is your expectation when you administer Vascepa to a severely hypertriglyceridemic patient in terms of the lipid effects those patients will experience?
A That the average patient, majority of my patients will achieve these lipid effects when I prescribe Vascepa.
Q So will the Vascepa labeling encourage clinicians to follow each step in the method claimed in claim 14 of the '715 Patent?
A Yes, for all the reasons that we've discussed.
Q Let's go to PX 30. And, Dr. Budoff, do you recognize this document?
A Yes. This is U.S. patent 8,431,560.
Q And is this one of the patents you analyzed in forming your opinions in this case?
A Yes.

MR. M. KENNEDY: Your Honor, plaintiffs Exhibit 30 is on the preadmitted list.

THE COURT: Yes.

BY MR. M. KENNEDY:

Q **Have you been informed that Amarin is asserting infringement of claims 4 and 17 from the '560 Patent?**

A **Yes.**

MR. M. KENNEDY: And, Mr. Brooks, if we could have PDX 2-42.

BY MR. M. KENNEDY:

Q **And, again, what does the notations in the Element Met column mean?**

A **So, again, just to reiterate, these are all -- all these elements have already been met based on our analysis of claim 1 of the '728 Patent.**

Q **Have you formed any opinions concerning whether the Vascepa label encourages clinicians to prescribe Vascepa to patients with severe hypertriglyceridemia wherein the administering effects a reduction in fasting triglycerides of at least about 10 percent without increasing LDL-C by more than 5 percent in the subject?**

A **Yes.**

Q **And what is that opinion?**

A **As we've discussed already, the effects in the subject, the triglyceride reductions, will be fasting triglyceride**

reductions, which is how the trials are done and how the methods are done, in practice, the fasting triglyceride levels will drop by 27 percent. So that's at least 10 percent.

LDL-C will go down by 5 percent in the subject, which is not a 5 percent increase, but rather a 5 percent decrease.

So all three of these elements will be met when physicians follow the label.

Q **And, again, these are -- you're referring to the data in the clinical study section of the Vascepa label that we've looked at?**

A **Yes.**

Q **When you administer Vascepa to a severely hypertriglyceridemic patient, do you expect to achieve results of the type claimed by claim 4 of the '560 patent?**

A **Yes.**

Q **When you administer Vascepa to a patient, do you achieve effects of the type claimed by claim 4 of the '560 Patent?**

A **Yes.**

Q **To the best of your knowledge, do clinicians prescribe with the intent to achieve the results -- the lipid effects -- the results of lipid effects claimed by claim 4 of the '560 patent?**

A **Yes.**

Q **So will the labeling encourage clinicians to follow each**

step in the method claimed in claim 4 of the '560 patent?
A Yes.
MR. M. KENNEDY: Okay. Then let's please look at PDX 244.
BY MR. M. KENNEDY:
Q And, again, is this asserted claim 17 of the '560 patent?
A Yes.
Q And what are you denoting with the notations in the Element Met column?
A Similar to the last few claims, again, these are the same language that was used and elements that were met based on the same analysis for claim 1 of the '728 Patent.
Q Have you formed any opinions concerning whether the Vascepa label encourages clinicians to prescribe Vascepa and expect to achieve effecting a reduction in fasting triglycerides of at least about 20 percent without increasing LDL-C in the subject compared to placebo control as required by claim 17 of the '560 Patent?
A Yes.
Q What is that opinion?
A That physicians following the label will see more than a 20 percent drop in fasting triglycerides, it dropped by 33 percent compared to control.
So that element will be met when they follow the label and look at the clinical trials section, they will see

that there is no increase in LDL-C compared to placebo control. So all of these elements will be met as physicians follow the label.

Q Dr. Budoff, do you administer Vascepa with the intent to effect reductions in fasting triglycerides of about 20 percent without increasing LDL-C in the subject compared to placebo control as required by claim 17 of the '560 patent?

A Yes.

Q When you administer Vascepa to patients with STG, do they achieve results in line with those required by claim 17 of the '560 patent?

A Yes.

Q Do other physicians prescribe Vascepa with the intent to achieve the lipid results claimed in claim 17 of the '560 patent?

A Yes.

Q So, in your opinion, will the Vascepa labeling encourage clinicians to follow each step in the method claimed by claim 17 of the '560 patent?

A Yes.

Q And then let's go to the PX 31, and this is -- Dr. Budoff, do you recognize this document?

A Yes, this is U.S. patent 8,518,929.

Q And is this one the patents you analyzed in forming your opinions in this case?

A **Yes.**
Q **You understand that Amarin is asserting claims 1 and 5 from this patent?**
A **Yes.**
MR. M. KENNEDY: And, Mr. Brooks, can we go to slide PDX 2-46.
BY MR. M. KENNEDY:
Q **And, Dr. Budoff, what have you shown on this slide?**
A **So, again, as previously stated, all of the elements will be met using the same analysis as claim 1 of the '728 Patent.**
Q **Does the Vascepa label instruct daily administration of Vascepa?**
A **Yes.**
Q **Daily administration of 4 grams of a pharmaceutical composition?**
A **Yes.**
Q **And will the labeling -- will the Vascepa labeling encourage clinicians to follow each step in the method of claim 1 of the '929 patent?**
A **Yes.**
Q **And then slide 2-47, this is claim -- asserted claim 5 of the '929 patent.**
And, again, Dr. Budoff, can you just very briefly explain what this slide shows.
A **Yes. So, again, the elements we just discussed in claim**

1 are met by the analysis of claim 1 on the previous slide,
and now there's two new elements here, "effective to reduce
apolipoprotein B in subjects."
Q Have you formed any opinions concerning whether the
Vascepa label encourages clinicians to administer Vascepa to
patients with severe hypertriglyceridemia effective to reduce
apolipoprotein B in subjects?
A Yes.
Q And what is that opinion?
A That the apolipoprotein B goes down in subjects as seen
in table 2 of the label, and physicians will be encouraged to
use Vascepa to reduce apolipoprotein B in their subjects.
MR. M. KENNEDY: And since we haven't looked at
apolipoprotein B quite as much today, Mr. Brooks, can we pull
up table 2 alongside this slide.
BY MR. M. KENNEDY:
Q And, Dr. Budoff, does table 2, the clinical study section
of the Vascepa label, support your opinion that the label will
encourage clinicians to administer Vascepa to reduce
apolipoprotein B in subjects?
A Yes, you can see that. Compared to baseline there was a
minus 4 percent reduction in apo B, and the overall difference
compared to placebo control is minus 9 percent, and it's
called out again in the sentence below the table, Vascepa 4
grams per day reduced median TG, VLDL-C, and apo B levels from

baseline relative to placebo.

Q **Dr. Budoff, do you prescribe Vascepa with the intent to reduce apolipoprotein B?**

A **Yes.**

Q **When you prescribe Vascepa, do you observe reductions in apolipoprotein B in your patients?**

A **Yes.**

Q **To your knowledge, do other clinicians prescribe Vascepa with the intent to reduce apolipoprotein B in the expectation that those reductions will be achieved?**

A **Yes.**

Q **So will the Vascepa labeling encourage clinicians to follow each step in the method claimed by claim 5 of the '929 patent?**

A **Yes.**

Q **And as with all the other Vascepa label related questions, if I ask you with respect to the Hikma and DRL labels, would you answer be the same?**

A **Yes.**

MR. M. KENNEDY: So I have no further questions for the witness at this time.

THE COURT: Thank you, Mr. Kennedy.

MR KLEIN: Your Honor, do you want to break or keep going?

THE COURT: Well, if I had my preference, we

would keep going, but I think we should take a lunch break at this time, so let's take a 30-minute lunch break. Thank you.

(The noon recess was taken.)

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RENO, NEVADA, TUESDAY, JANUARY 14, 2020, 1:04 P.M.

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THE COURT: Please be seated.

Mr. Klein?

MR KLEIN: Thank you, Your Honor.

Good afternoon, Dr. Budoff.

THE WITNESS: Afternoon.

MR. KLEIN: We obviously met at your deposition, but, for the record, I'm Charles Klein, and I will be asking you some questions on behalf of the defendants.

CROSS-EXAMINATION

BY MR. KLEIN:

Q Each asserted patent in this case requires using icosapent for at least 12 weeks. You understand that, right?

A Yes.

Q Okay. And defendants' product labels do not specifically encourage using icosapent for at least 12 weeks, correct?

A No, they do.

Q They specifically encourage using icosapent for at least 12 weeks?

A Yes.

Q Okay. Let's take a look at the indication. And for the record, you recognize the top snapshot as DX 2248? That's the Vascepa MARINE indication?

A **Yes.**
Q **Okay. And we're not going to talk about -- you understand there's a new indication, right?**
A **Yes.**
Q **Okay. We're not going to talk about that other indication today so if I refer simply to the Vascepa indication, can we understand that we're talking about the MARINE indication?**
A **Yes.**
Q **Okay. And then we have the Hikma indication, which is DX 2256, and the DRL indication which is DX 2266, and I believe on direct you testified that these three indications are materially identical, correct?**
A **Yes.**
Q **All right. Neither the Vascepa indication nor defendants' indications is actually telling doctors to use the drug for at least 12 weeks, right?**
A **It does not state 12 weeks, that's correct.**
Q **Right. Right. And if we look at the dosage and administration section, and here I've got the Hikma label, DX 2256, on the screen, but do you understand that the DRL label is materially identical?**
A **Yes.**
Q **Okay. And the dosage and administration section in defendants' labels doesn't specify any duration of treatment,**

correct?
A Correct.
Q And so defendants' dosage and administration section doesn't specifically encourage using icosapent for at least 12 weeks, right?
A Correct.
Q In fact, there's no explicit instruction in the Vascepa label or in defendants' labels to use icosapent for at least 12 weeks, right?
A No, there is explicit language.
Q There -- listen carefully to the question, please.
Is there -- there is no explicit instruction anywhere in the Vascepa label or in defendants' labels telling doctors to use icosapent for at least 12 weeks.
A There is explicit language in the Hikma and DRL labels instructing physicians to use Vascepa or icosapent ethyl for 12 weeks.
Q So what language are you referring to?
A The clinical trials section.
Q Okay. We'll get to that later, but the clinical trials section is describing a 12-week study, the MARINE study, right?
A Well, I was just trying to answer your question.
My understanding of the infringement is the label taken in its entirety. So when you ask me does the label

state 12 weeks, and I say yes, I believe I'm correct.
Q And we'll get to the clinical trial section later in the examination, but just to make sure we're on the same page, the clinical trial section of defendants' labels does not say, doctors, you should give the drug for at least 12 weeks. Can we agree on that?
A It does not say those words, that's correct.
Q And instead, the Vascepa label, as well as defendants' labels, leave it entirely up to the physician's discretion to determine the duration of treatment, correct?
A Yes.
Q Now, so, what that means is defendants' labels will allow doctors to tailor treatment duration to the individual patients, correct?
A Yes, but they have to be concordant with the disease that's indicated.
Q Right. Of course. But doctors can follow defendants' labels and prescribe icosapent indefinitely if they want. That's your opinion, right?
A Yes.
Q But a doctor could also prescribe icosapent for only ten weeks, if that's what's called for, for the particular patient and the patient concerns, correct?
A I can't imagine that scenario, but if that scenario existed, then yes, I agree.

Q Okay. Then we'll come back to that.

Either way, the labeling gives this decision, the treatment duration, to the doctor to make, right?

A Yes.

Q And so it would be entirely consistent with defendants' labels for a doctor to prescribe icosapent for less than 12 weeks, right?

A Yes.

Q Now, we talked about how there's no explicit instruction in the labels that actually tells doctors you should use icosapent for at least 12 weeks. Do you remember that?

A Yes. I believe I feel there is explicit language, and you feel there is not. But, yes, I remember that previous discussion we just had.

Q Okay. But I think you said there's no explicit language that actually tells doctors you should use this product for at least 12 weeks, correct?

A Your quote is not in the label, I agree with that.

Q Right. You're referring to the 12 weeks term in the clinical studies section, right?

A Yes, which I believe instructs physicians to use it for 12 weeks.

Q Okay. So your opinion really is, when doctors read the label as a whole, including the 12 weeks statement in the clinical studies section, that will apply to doctors that they

should go ahead and use the drug for at least 12 weeks, right?
A Yes.
Q On the screen is DX 2256 and, for the record, it's DDX 3.3. This is -- you recognize this as the indications and usage section of Hikma's proposed label, right?
A Yes.
Q And, obviously, as -- the indication is for severe hypertriglyceridemia, right?
A Yes.
Q And your opinion is that doctors know that this is a chronic condition?
A Yes.
Q Okay. And your opinion is that the condition, severe hypertriglyceridemia, requires indefinite drug therapy, right?
A Yes.
Q Okay. I want to make sure I understand what you're saying. Are you saying that doctors will read defendants' indication as necessarily, in all circumstances, requiring indefinite treatment?
A No.
Q And why do you say no?
A Well, not everybody can tolerate therapy forever so we never use absolutes, but I would say doctors will read this label and say, oh, severe hypertriglyceridemia, that's a chronic condition, I'm going to treat this chronically.

To say that in every case they use it indefinitely is, obviously, not possible. Some patients don't tolerate therapy, some patients can't get therapy, so we can't use absolutes when we talk about what a person of ordinary skill in the art will do in a given situation.

Q **Okay. And we'll come back to that concept.**

I want to direct you to paragraph 357 of plaintiffs' proposed findings of fact, and this is ECF number 331.

You probably haven't seen this, but I will represent to you that this is a statement from plaintiffs' to the Court last week, and in this proposed findings of fact, plaintiffs propose that the Court find that clinicians will read defendants' labeling with the understanding that severe hypertriglyceridemia is almost invariably a chronic condition.

Do you see that?

A **Yes.**

Q **And as a matter of linguistics, almost invariably isn't always, right?**

A **Correct.**

Q **Okay. And so is this consistent with your testimony that it's almost invariably a chronic condition?**

A **Yes.**

Q **Okay. And so you're not testifying that severe hypertriglyceridemia is always a chronic condition, correct?**

A **Correct.**

Q **And do you understand that defendants' labels never actually say that severe hypertriglyceridemia is a chronic condition, right?**

A **Yes. I think Dr. Ketchum went through that yesterday.**

Q **Yeah, I was just going to bring that up. You were here, right?**

A **Yes.**

Q **And you understood that there was a proposal to the FDA from Amarin to characterize the Vascepa patient population as requiring chronic care, but FDA rejected that, right?**

A **Yes.**

Q **But your opinion is that a doctor would see the indication and understand that severe hypertriglyceridemia is very often a chronic condition, right?**

A **Yes.**

Q **Okay. And so what you're really saying is that a doctor knows that severe hypertriglyceridemia can be a chronic condition, not that it always is a chronic condition, right?**

A **I think we keep changing the adjectives, but why don't we stick with almost invariably just to be concise because we've gone from almost invariably now to can.**

Q **Okay.**

A **Which I think is a pretty broad change in terminology. So I'll stick with this language as language that I'm comfortable with.**

Q **Okay. Well, you agree it's not always a chronic condition, right?**

A **That's correct.**

Q **So just as a matter of logic, what you're saying is it can be. Now, in your view, it is almost invariably, but you're really saying it can be a chronic condition, correct?**

A **It is a chronic condition in almost all cases, but not all cases.**

I described the reversible causes earlier, diabetes out of control, binge drinking, hypothyroidism, as other causes that can push people up into the severe hypertriglyceridemic range that would not be considered a chronic condition.

Q **Okay. Thanks. You're getting to my next point.**

So you were here for opening statements as well, right?

A **Yes.**

Q **And did you see this testimony from Dr. Toth during the opening statements?**

A **Yes.**

Q **And you know who Dr. Toth is, right?**

A **Yes.**

Q **You understand he's one of Amarin's experts in this case.**

A **Yes, I know Dr. Toth.**

Q **Yeah, you actually know him otherwise as --**

A **Yes, we are -- we are on different guidelines and committees together.**

Q **And so you saw that Dr. Toth testified in his deposition that there would be circumstances where very high triglycerides was an acute phenomenon, right?**

A **Yes.**

Q **And you agree with that?**

A **Yes, for the reasons I've already stated.**

Q **Right. And that's what you meant by the reversible causes?**

A **Yes.**

Q **Okay. And doctors would know from reading defendants' indications that sometimes severe hypertriglyceridemia can be an acute phenomenon, right?**

A **Yes.**

Q **Did you also see this testimony from Dr. Peck?**

A **Yes.**

Q **Do you know Dr. Peck?**

A **No, not outside of this context.**

Q **Okay. But you understand that Dr. Peck is Amarin's regulatory expert in this case?**

A **Yes.**

Q **And so you saw that Dr. Peck said he doesn't think that the indicated use of Vascepa is limited to chronic use, right?**

A **Yes.**

Q **Okay. And you're not an expert in FDA regulations, correct?**

A **Correct.**

Q **So you agree with Dr. Peck's testimony when he says, "I don't think the indicated use of Vascepa is limited to chronic use." Correct?**

A **I disagree with that.**

Q **You disagree with what -- so you think Dr. Peck is not accurately characterizing the indication from an FDA regulatory perspective?**

A **I didn't have a chance to discuss with Dr. Peck. It would be -- I don't know, I think you guys throw around the word hearsay -- for me to take this at face value without any context.**

But I believe, if you're asking my opinion, that the current indicated use of Vascepa, you're supposed to systematically eliminate all of the acute causes, that's clearly listed in the label, and then the resultant treatment, the resulted indication for Vascepa is, after you've removed all of the acute indications, you use Vascepa which would leave only chronic use.

So my reading of the label -- and I'm not arguing with Dr. Peck, but my reading of the label is that the current indicated use of Vascepa is for the resultant people who have genetic problems, and thus it is a chronic condition.

Q **Okay.**
A **So it's only indicated to -- for chronic use.**
Q **And we'll unpack that a bit.**
But what I'm getting at here is you're offering that opinion from the perspective of a physician who will apply the label, correct?
A **Yes.**
Q **Okay. And do you understand that Dr. Peck is offering an opinion from the perspective of what FDA approved?**
A **Yes. Again, I wasn't there. I didn't read Dr. Peck's full deposition transcript. I see it referenced here, so I really don't think I can speak to this one sentence.**
But my opinion is I agree with Dr. Peck on this one question. I would answer it differently.
Q **Okay. But you are not an FDA regulatory expert, right?**
A **That's been established.**
Q **And you're not expert in FDA labeling, right?**
A **That's been established.**
Q **So if Dr. Peck testifies from the FDA perspective that FDA did not limit the indication to chronic use, you would have no basis to dispute that, correct?**
A **I would not argue with Dr. Peck on the FDA, but I believe we already heard about the FDA, and it said should it be used for acute use, and the answer was not applicable.**
So, again, my reading from yesterday, and my

understanding of what the FDA already opined on, is that it's not appropriate for acute use because they said not applicable. That was in the questions in the FDA documents that were presented yesterday.

But, again, I'm not going to get into an FDA argument with Dr. Peck.

Q And just to be clear, you're referring to the form that was used in Dr. Ketchum's testimony?

A Yes.

Q You did not offer any opinions on that form in your report, correct?

A No.

Q And you're not offering any opinions on that form today, correct?

A I'm only trying to answer your question as best I can.

Q Okay. But -- so you say you disagree with Dr. Peck at least from a physician perspective, but you do agree it would be consistent with the Vascepa labeling for a doctor to prescribe Vascepa for fewer than 12 weeks, correct?

A Yes.

Q Let's go back to the indication, and, again, I'm using Hikma's indication for simplicity, but you understand DRL's indication is the same, right?

A Yes.

Q And we talked about this a moment ago.

You are relying on the term severe hypertriglyceridemia in the indication as signaling to doctors that they should use the drug long-term, correct?

A **Yes.**

Q **Okay. Now, let's focus on that term.**

The term severe hypertriglyceridemia has a well-known meaning to doctors who treat the condition, right?

A **Yes.**

Q **And the meaning of severe hypertriglyceridemia is actually in the indication. It means greater than or equal to 500 milligrams per deciliter, right?**

A **Yes.**

Q **And that's it. That's -- that's the definition of severe hypertriglyceridemia, right?**

A **Well, no. I mean, there's definitions of diseases. This is not a definition. This is just stating the term, severe hypertriglyceridemia.**

But, yes, it's characterized by triglycerides greater than 500 milligrams per deciliter in the blood in the fasting state. But, yes, that's -- that's what I construe to be severe hypertriglyceridemia.

Q **Right. And that is how doctors diagnose severe hypertriglyceridemia. They have a blood test taken, and if the triglycerides are above 500, then the doctors conclude the patient has severe hypertriglyceridemia, right?**

A **Yes.**
Q **Okay. And severe hypertriglyceridemia has various causes, right?**
A **Yes.**
Q **And the diagnosis of severe hypertriglyceridemia does not turn on the cause, right?**
A **That's correct.**
Q **So as long as the patients have triglyceride levels above 500, regardless of why, they have severe hypertriglyceridemia.**
A **Just to be concise, I would say fasting triglycerides greater than 500, that's the definition.**
Q **And that's a fair point. And let's just assume, when we talk about the triglyceride levels, that we're talking about fasting levels. I think that's a fair characterization.**

And doctors know that when patients have triglycerides above 500, the goal is to prevent an acute pancreatitis attack, right?
A **Yes.**
Q **Okay. And so the indication is signaling to doctors that if the patient has triglycerides above 500, no matter the cause, that icosapent can be used in that patient, right?**
A **No, that's not how I read the label. I read the label as you must exclude acute causes, and then you would use Vascepa. That's how I read the label, and that's how I believe physicians read the label.**

Q **Okay. And you're referring to the dosage and administration section, right?**

A **Yes. But when you say the label, I'm taking the label -- again, my understanding of infringement is the label taken in its entirety.**

So I don't think it would be fair to say, "Doctor, you're only allowed to read the first line. Now what do you want to do with your patient?"

Q **Okay. No. And that's a fair point, Doctor, and we'll get to the doseage and administration section, but for now let's focus on the indication itself.**

A doctor looking at the indication would understand that if the patient presents with triglycerides over 500, then icosapent can be used in that patient subject to, you know, other instructions in the label, correct?

A **Yes.**

Q **And a doctor would understand that if icosapent is being used, it will be used as an adjunct to diet, right?**

A **Yes.**

Q **And the hope is that using icosapent as an adjunct to diet will avoid pancreatitis.**

A **Yes.**

Q **All doctors who treat severe hypertriglyceridemia understand when they read the indication of Vascepa or defendants' labels, that that's the goal of using the drug,**

right?
A That is at least the primary goal, yes.
Q Yes. Well, okay.
Let's go to the ATP III guidelines, and you talked about this on direct, right?
A Yes.
MR. KLEIN: And, for the record, this is DX 1526, page 28, and the document has been admitted into evidence.
BY MR. KLEIN:
Q Now, the ATP guidelines explain that when triglycerides are very high, greater than or equal to 500, the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering, and you agree with that, right?
A Yes.
Q Okay. And that's the primary treatment aim regardless of why the patient has triglycerides above 500, right?
A Yes.
Q If we go to the next slide, which is DDX 3.9, we're on DX 1526, page 28, the guidelines go on to say this approach -- in other words, the aim of preventing acute pancreatitis through triglyceride lowering -- requires very low fat diets, weight reduction, increased physical activity, and usually a triglyceride-lowering drug, and I omitted the parentheticals, right?

A **Yes.**
Q **And this approach is consistent with your own practice, right?**
A **Yes, except they don't stipulate -- they don't -- this is pre-2002, this was pre-Vascepa, so the only two choices given here are fibrate and nicotinic acid, and now we have two other drugs that are for this indication. But, yes.**
Q **Okay. Yeah. Putting aside the specific drugs, this statement in the ATP III guidelines is consistent with your practice, right?**
A **Yes.**
Q **And to be clear, the guidelines here say the approach focuses on diet, weight reduction, increased physical activity, and usually a triglyceride-lowering drug, right?**
A **Yes.**
Q **Okay. And the guidelines don't tell doctors if patients present with severe hypertriglyceridemia, you should always use drug therapy, correct?**
A **That's correct.**
Q **And that, too, is consistent with your own practice, right?**
A **Yes.**
Q **Okay. Let's go to the next slide, and I'm just highlighting a different sentence on the same page.**
The guidelines then say only after triglyceride

levels have been lowered to less than 500 milligrams per deciliter should attention turn to LDL lowering to reduce risk for CHD, right?

A **Yes.**

Q **And, in other words, once the triglyceride -- once the triglyceride levels in a patient dip below 500, you become less concerned about pancreatitis and your focus turns to cardiovascular treatment, correct?**

A **Yes, and I've tried to outline that today in the direct testimony as well.**

Q **Okay. And I think you talked about this as well, this is how the ATP III characterizes the different levels of triglycerides, right?**

A **Yes.**

Q **Okay. And high triglycerides are 200 to 499, right?**

A **Yes.**

Q **Okay. And some patients are in this range, the high triglyceride range, because of generic -- genetic factors, correct?**

A **Yes.**

Q **And -- but even if a patient has triglycerides over 500, and you're able to reduce the pancreatitis risk by getting the triglycerides into the very high -- into the high triglyceride range, you still want to get those levels lower, right?**

A **I think we know a lot more now also given the results of**

the REDUCE-IT trial. But, yes, I think that is -- still I would still like to get the triglycerides lower than 499.

Q **You would like to get them lower than 200, right?**

A **Yes.**

Q **But that goal, that desire, is based on cardiovascular risk, not pancreatitis risk, correct?**

A **That's correct.**

Q **And you understand that the goal with regard to severe hypertriglyceridemia is not -- the primary goal is not to reduce cardiovascular risk but to reduce the acute pancreatitis risk, right?**

A **Yes.**

Q **Okay. And defendants' products are not indicated to reduce triglycerides in patients who have baseline levels below 500, right?**

A **Correct.**

Q **And so a doctor using Vascepa or defendants' products, should they come to market, solely to reduce cardiovascular risk would be using icosapent off label, again, ignoring the new REDUCE-IT indication.**

A **Yes.**

Q **And so you understand defendants' products are not indicated to improve cardiovascular outcomes, right?**

A **Correct.**

Q **And you also understand -- although I don't think it came**

up during your direct, but you understand that defendants are carving out this second REDUCE-IT indication from their proposed labels, right?

A **Yes.**

Q **Now, we talked about how there can be various causes of very high triglycerides, right?**

A **Yes.**

Q **And most commonly severe hypertriglyceridemia is caused by unhealthy diet and poor lifestyle choices, right?**

A **No, most commonly it's caused by genetics. We've reviewed that, I think, a few times.**

Q **Now, when you say genetics, there are really two different types of genetic -- genetic causes of severe hypertriglyceridemia. For example, there are some genetic causes that, no matter what you do with diet and exercise, you are absolutely going to need drugs, correct?**

A **Yes.**

Q **And these patients generally have triglycerides well above 500, right?**

A **The more severe the genetic abnormality, the higher the triglyceride levels will go, yes.**

Q **I mean, we're talking sometime 1,000 or even 2,000, correct?**

A **Yes.**

Q **Okay. And the -- these conditions include familial**

hypertriglyceridemia; is that right?
A Yes.
Q And familial combined hyperlipidemia; is that right?
A That's usually represented by -- combined implies that multiple di -- there's multiple problems and usually the triglycerides are not as high and their LDL, their bad cholesterol is also high.

So there are, again -- I mean, I listed some of the -- I think scientific statement from the American Heart Association talked about the seven most common genetic abnormalities.
Q Okay. And another one is defects in lipoprotein lipase or apo C-2, right?
A Yes.
Q Okay. But these types of genetic disorders where the patients have triglycerides at the 1,000, 2,000 level, these are pretty rare, right?
A Some of those specific ones are pretty rare, but some of them are what we call incomplete transmissions.

So, for example, somebody could have a triglyceride level 550 or 600, and if we were to do genetic testing, we might find that they have a partial -- partial expression of that problem.

In other words, they don't have to be pure -- kind of like not be purebreds per se in the regard to that

disorder. But the patients who have pure genetic disorders, they tend to have very high triglycerides as you're describing.

Q And that is rare.

A That is rare.

Q Okay. Now, with regard to the patient population who has very high triglycerides, it's less rare for patients to have a genetic predisposition to high triglycerides, and then there are other factors that cause them to go above 500. Is that fair?

A Yes.

Q Okay. And that's where diet and lifestyle can come into play.

A Yes.

Q All right. Okay. Let's go to slide DX 3.13, which is DX 1982, and I don't believe this is in evidence, so I would move -- do you recognize this as Amarin's website for Vascepa?

A I don't know if I've seen this, but I would take your word for it that it is. It looks like it.

MR KLEIN: I move to admit DX 1982.

MR. M. KENNEDY: No objection, Your Honor.

THE COURT: That request is granted.

(Defendants' Exhibit 1982 received in evidence.)

BY MR. KLEIN:

Q Now, here you can see that -- and I'll represent to you

that we took this from Vascepa.com, and you'll see that the title of this portion of the web page says what are the causes?

A Yes.

Q And according to Amarin's Vascepa website, there are five causes listed, right?

A There are five listed here, yes.

Q And the first one is diet. Do you see that?

A Yes.

Q And I circled "especially alcohol." You agree that diet, especially alcohol, with be a cause of severe hypertriglyceridemia, right?

A Yes.

Q Okay. And the second one is lack of exercise, that's also a common cause of severe hypertriglyceridemia?

A It tends to be a contributing factor. I think -- I don't think lack of exercise by itself is considered a primary cause, but I think it would contribute so we recommend exercise to help lower triglycerides.

Q It's normally discussed in combination with diet. Is that fair?

A Yes.

Q And then the third cause is medical conditions, right?

A Yes.

Q And I think you talked about that, for example, a patient

could have diabetes and that might cause severe hypertriglyceridemia?
A Yes.
Q But if the diabetes is controlled, that might address the severe hypertriglyceridemia.
A That is the guidelines and my recommendation, yes.
Q Okay. And then there's specific drugs. I think talked about that as well, right?
A Yes.
Q And we'll get back to that.
And then genetics is the fifth cause listed on Vascepa.com, right?
A Right.
Q Now, the defendants' indication and labels are not limited to addressing the genetic issues that we talked about that can cause triglycerides to be way up in the 1,000, 2,000 area, right?
A That's correct.
Q Yeah. Defendants' labels would include very high triglycerides caused by any of these five factors, diet, exercise, medical condition, specific drugs, or genetics, correct?
A No.
Q Okay. So you're saying that the Vascepa.com website is incorrect?

A **No. Vascepa -- this is saying what are causes of very high triglycerides, and they list five different causes.**

The label, and, again, the label taken in its entirety, tells you to address diet and exercise first and eliminate those causes, to address medical conditions and eliminate those causes, to look for specific drugs and eliminate those causes; and then, if their triglycerides are still high, to treat.

So if you looked at your chart and you crossed out those other four, the only thing left to use Vascepa on label would be genetics.

Q **Okay. I want to make sure I understand this testimony.**

You're saying that the indication requires doctors to eliminate the first four causes on Vascepa.com, diet, exercise, medical conditions, specific drugs, and use the drug only if genetics is the sole cause. Is that your testimony?

A **No, I'm saying that the label eliminates those other 4, and then says if severe hypertriglyceridemia still exists, you then prescribe Vascepa.**

Q **Are you saying, Doctor, that if -- if a patient presents to a physician, and has triglycerides of 550, and the doctor says, "I -- I want you to go on a diet, and I want you to exercise, and I want you to start Vascepa right away," you're saying that's an off-label use?**

A **No. You're supposed to institute diet and exercise first**

and then Vascepa.

Q Okay. But it's not an off-label use if the doctor at that first visit says, "I want you to change your diet, I want you to exercise, and I want you to fill this prescription," right, sir?

A I mean, you can interpret that as saying, well, I said the word diet and exercise first so it preceded it, but that's not the intent of the FDA nor the guidelines. The guidelines say institute diet and exercise and then prescribe Vascepa.

So instituting, to me, is not saying, "Mr. Johnson, you should really eat better. Here's a prescription."

I don't believe that meets the term institute, and it's not how the guidelines are written. We just went through the ATP III guidelines. They say to address diet first and then prescribe Vascepa.

And I think the label is pretty clear in that language that you should institute diet and exercise first before initiating Vascepa.

There's literally a section, 2.1, that says what to do before initiating Vascepa. So it's telling you to do that specifically. That's not my interpretation. That's got to be the exact way that the label is encouraging physician's use.

Q Okay. Well, let's start with this. The Vascepa labeling is not limited to reducing triglycerides in patients who have a genetic predisposition to high triglycerides, right?

A **That's true.**
Q **Okay. And nothing in the Vascepa label discusses genetic causes of severe hypertriglyceridemia?**
A **That's true.**
Q **And the cause of severe hypertriglyceridemia in most patients is not solely genetics, right?**
A **Well, again, by the time we get to -- we're talking about on-label use, I believe it is largely genetics. If we're talking just about anybody who has ever had a fasting triglyceride of 501 more, or 500 or more, that could be a combination of factors, I agree with you.**
Q **Okay. Let's put aside whether it's on-label or off-label now, and we'll talk turn that next.**
A **Sure.**
Q **Just doctors understand that when patient -- the patient population that has very high triglycerides, a large portion of that population has very high triglycerides for reasons not solely related to genetics. Fair?**
A **Yes.**
Q **Okay. In fact, at least a third of the patient population with severe hypertriglyceridemia has the condition for reasons not solely related to genetics, right?**
A **I think that would probably be correct. Yes.**
Q **And the other causes would include things like diet and exercise are not ideal, correct?**

A **Yes.**

Q **Okay. Let's go to -- let's fast forward and go to the dosage and administration section because that's what you were focusing on.**

Okay. And this is DX 2256 for the record.

Do you recognize this as the dosage and administration section from Hikma's proposed label?

A **Yes.**

Q **And you testified that the dosage and administration section instructs doctors to eliminate other causes of high triglycerides before prescribing icosapent, right?**

A **Yes.**

Q **Okay. Let's walk through what each section says. The title -- and I'm focusing on 2.1. That's what you're focusing on, right?**

A **Yes.**

Q **The title says Prior to Initiation of Icosapent Ethyl, right?**

A **Yes.**

Q **And then the first thing it says to do is assess lipid levels before initiating therapy, and I think you testified that, you know, that's -- that just makes sense, it's standard, you have to take a test, right?**

A **Yes.**

Q **Okay. Then it says identify other causes, e.g.,**

diabetes, hypothyroidism, or medications of high triglyceride levels, and manage as appropriate, right?

A Yes.

Q So this is telling doctors look to see if there are other causes, right?

A Yes.

Q And if the doctors identify other causes, the label leaves it up to the discretion of the doctor to manage as the doctor feels is appropriate, right?

A Yes.

Q Okay. The label is not telling, in this first bullet, the label is not telling doctors don't give icosapent yet, address those other factors first. Agreed?

A Correct.

Q Okay. And that bullet certainly isn't saying only give icosapent if absolutely necessary and the only causes are genetics, right?

A That's correct.

Q And when the label, 2.1, first bullet says manage as appropriate, that is giving doctors wide discretion to do what the doctor sees fit for the individual patient.

A Yes.

Q Okay. Let's go to the second bullet.

The second bullet says patients should engage in appropriate nutritional intake and physical activity before

receiving icosapent ethyl which should continue during treatment with icosapent ethyl, right?

A Yes.

Q And what this bullet is saying is that doctors should make sure they don't use icosapent as a substitute for diet and exercise, right?

A No, they're saying that patients should try a trial of nutritional intake and physical activity before receiving icosapent ethyl.

It says they should engage in appropriate nutritional intake and physical activity before receiving the drug.

So saying eat well, exercise, and here's a prescription, would not be following Hikma's proposed label because they wouldn't be engaging in any of those things before receiving icosapent ethyl.

Q Okay.

A So I believe that if you don't give the patients a trial of diet and exercise before receiving icosapent ethyl, that that would be perceived as an off-label use of the drug.

Q Okay. So your opinion is that doctors should never prescribe icosapent without first making sure that the patients engage in diet and exercise?

A You can vary from the label. Doctors have discretion. But the label specifically tells you that they should engage

first.

So if you are following the label, an on-label use would be a trial of diet and exercise, we've discussed that a few times today, and then if they fail appropriate diet and exercise, then you prescribe icosapent ethyl.

Q That's not how you practice, right?

A That's how I largely practice.

Q When a patient comes to see you and presents with very high triglycerides, you hold off on prescribing Vascepa until the next visit?

A If their triglyceride are 550, like in your example, and they have a terrible diet, yes. I would say let's clean up your diet and exercise and see if we don't get there without therapy, and if we don't get there without therapy, then I'm going to need to prescribe a medication.

That's how we all prescribe therapy. That's the common use of all treatments. Blood pressure pills are the same. When I see somebody with high blood pressure, and they have a high salt diet, I say let's try diet and exercise and see if your blood pressure comes down, and if that fails, I'm going to have to write you a prescription for a blood pressure pill.

Q Okay.

A That's the way the FDA literally says -- there's no -- I don't think there's any interpretation here. Patients should

engage in appropriate nutritional intake and physical activity before receiving icosapent ethyl. Your company wrote a -- very clear instructions for doctors to follow.

Q Okay. Doctor, you prescribe icosapent the first time you see a patient who presents with very high triglycerides, right? That happens?

A Sometimes, sure.

Q Probably most of the time, right?

A I don't know. I haven't looked back exactly. But some of my patients are already engaged in appropriate nutritional activity and nutritional intake when they first see me.

I described a scenario today of a young woman who is already doing all the right things, and her triglycerides are too high. So she already engaged in appropriate nutritional intake and physical activity before receiving icosapent ethyl, and then I prescribed it. That's my first visit, but the patient is already doing what the label instructs me to do.

Q Okay. And pancreatitis can be a life-threatening condition, right?

A Yes.

Q And if a patient presents to you with 650, for example, you're not going to hold off on giving that patient Vascepa for -- until you see the patient a second time, you're going to prescribe Vascepa right away, correct?

A In most cases, yes.

Q Yes. And are you really telling the Court that the Vascepa label and defendants' label will make it an off-label use if a doctor prescribes Vascepa at the same time as the doctor instructs the patients to improve their exercise and diet?

A I believe, and I think the label is explicitly clear here, that if you think diet and exercise is all they need, then you should not be prescribing Vascepa.

So in your first example where the triglycerides are 550, and they have a terrible diet, I would not, and the label would not advocate to put them on Vascepa because it is highly likely that diet and exercise intervention alone will not achieve the target.

Now, if somebody has triglycerides of 2,000, and their blood is turning white from fats, then I do not wait. But I think that that could be perceived as an off-label use.

Regardless, the vast majority of patients we see, we're supposed to first address nutritional intake and physical activity before receiving icosapent ethyl, and then, if they don't get under 500, we then prescribe them the therapy.

That's also how the MARINE trial was done which I testified to this morning on how we did the MARINE trial, how the trial was performed by having a 6-to 9-week trial of diet and exercise before prescribing therapy.

Q **Okay. Let's take another look at the language in the second bullet.**

So would you -- your entire opinion here is based on one term, the term "before," right?

A **No, my entire opinion is based on my experience, treatment, and training. The word "before" --**

Q **No, no, hold on. Just to be clear --**

A **-- is contributory towards that. My opinion is never based on a single word.**

Q **No, no, just --**

A **I want to be clear for the court.**

Q **Okay. All right. But your opinion with regard to what's on-label and off-label in view of 2.1 -- bullet 2, turns on the word before, right?**

A **In this one scenario, yes.**

Q **I mean, if that said "with," you would have a different opinion, right?**

A **I think the implication would be different, yes.**

Q **And when 2.1 bullet two uses the term before, it doesn't specify any time frame, right?**

A **That's true.**

Q **It doesn't say, doctors, make sure that the patients actually improve their diet and exercise for 12 weeks, come back, and then if it's clear that the causes are genetic, then you may prescribe icosapent. That's not what the label is**

saying, right?
A It doesn't give a time period, that's correct.
Q And, in fact, and I think you mentioned something like this earlier, if the doctor told the patients I want you to -- here's a diet, I want you to follow it, here's exercise, regimen I want you to follow it, here's a prescription, fill it when you can get to a pharmacy, that would be following the dosage and administration section 2.1, bullet 2, correct?
A No.
Q And why is that?
A Another word in the label it says engage, so they should engage in appropriate nutritional intake and physical activity. It doesn't say a doctor should advise that you go on diet and exercise, and here's a prescription. It says that they should engage in appropriate nutritional intake and physical activity before receiving icosapent ethyl.

I don't think you can change the meaning of that. I think doctors would read that and understand that you should give them a trial. It doesn't have to be exactly 12 weeks as you outlined in your previous example, but you need to give them a trial of diet and exercise, and if they fail that, then they can receive icosapent ethyl if their triglycerides are still above 500.
Q Now, Dr. Budoff, the most common practice is for doctors to prescribe icosapent as a first step for patients with

triglycerides above 500, correct?
A I don't know that.
Q Okay. Actually you do. Let's go to DX 1554, paragraph 56. Let's go first to the first page so we can identify the document.
Okay. You recognize DX 1554 as your opening report?
A Yes.
Q Okay. Now let's go to page 17, paragraph 56.
A I'm sorry, what paragraph?
Q Paragraph 56.
A Okay. It's not on the screen?
Q It will be there in a second.
A Sure.
MR KLEIN: This is the reply? Do I have the wrong document?
No, this is right.
BY MR. KLEIN:
Q Okay. Here, in your opening report, you said,
"For elevated lipids, therapy guidelines, including ATP III, recommend diet and lifestyle modification, and for patients with triglycerides of 500 milligrams per deciliter or higher, given the serious risk of pancreatitis and a recognition that lifestyle counseling alone is often insufficient for these patients, physicians most commonly recommend a

triglyceride-lowering medication, along with lifestyle counseling, as the first step."

Was that in your report, sir?

A No, that's citing ATP III, that's correct. That's 2002. I don't believe that's an on-label use.

Q Okay. So you're saying this statement in your opening report is inaccurate?

A No, I'm not saying that it's inaccurate at all. I'm saying that it's -- I don't perceive it to be an on-label use if you prescribe the drug at the same time as diet and exercise and you don't have them engage in nutritional intake and appropriate physical activity before receiving icosapent ethyl.

Q Okay. Let's take a look at your reply report, and you submitted a reply expert report after Dr. Sheinberg responded to your report, right?

A Yes.

Q So this is after Dr. Sheinberg raised the 12-week noninfringement defense, right?

A Yes.

Q Okay. And you recognize DX 1556 is your reply report?

A Yes.

Q Okay. Let's first take a look at paragraph 54.

In paragraph 54 of your reply report you said, "I disagree that clinicians would read the indications and usage

section as encouraging clinicians to treat hypertriglyceridemia by providing the patients with a prescription for Vascepa or one of defendants' proposed ANDA products but instruct the patient not to begin taking the medication until after improving their diet and exercise regimen over the course of 4 to 6 weeks."

Right? Is that something you said in your reply report in response to Dr. Sheinberg's report?

A Yes.

Q Okay. Let's also take a look at paragraph 57 of your reply report.

All right. In paragraph 57, you start off by talking about the treatment guidelines, and in the second sentence you say,

> "The treatment guidelines therefore advise that clinicians immediately treat severely hypertriglyceridemic patients with triglyceride-lowering pharmacotherapies."

Right? Is that what you said?

A Yes.

Q Immediately treat, right?

A Yes.

Q Okay. And if we go to paragraph 209 of your reply report, here you say that,

> "Statements in the label acknowledge that

clinicians will generally recommend to their severely hypertriglyceridemic patients that they improve their diet or improve or begin an exercise regimen. However, in cases where the risk of pancreatitis is judged sufficiently immediate, pharmacotherapy will begin immediately."

This was in your reply report as well?

A Yes, that's exactly the scenario I just gave you. I said if the triglyceride are superhigh --

Q Sir, I -- Doctor, I just asked you whether that was in your report.

A Okay. I was just trying to put it in context, but, yes.

Q Okay. And according to ATP III, if patients have triglycerides above 500, they're at risk for pancreatitis, correct?

A Yes, they are at risk for pancreatitis.

Q And putting aside all of your testimony with regard to the dosage and administration section that we were talking about, a clinician -- it would be consistent with the Vascepa labeling, and thus defendants' labels, for a doctor to prescribe icosapent ethyl for fewer than 12 weeks, correct?

A Yes.

MR. KLEIN: Now, we were talking about the various causes -- can you go back to the PowerPoint and DDX 3.14.

BY MR. KLEIN:

Q We were talking about various causes of severe hypertriglyceridemia, and we looked at the Vascepa.com website. Do you remember that?

A Yes.

Q Okay. I want to now turn to the Miller article which you talked about on direct. Do you remember that?

A Yes.

MR. KLEIN: Okay. And for the record, I'm referring to DX 1632, and I believe the same document PX 269 has already been admitted, but for the -- to avoid any confusion we'll move to admit DX 1632.

MR. M. KENNEDY: No objection.

THE COURT: 1632 is admitted.

(Defendants' Exhibit 1632 received in evidence.)

BY MR. KLEIN:

Q And we're at 1632, page 11. Do you remember talking about this?

A Yes.

Q Okay. And you understand -- do you understand that Dr. Miller was actually Amarin's claim construction expert in this case?

A I'm not aware of that, but I'll take your word for it.

Q Okay. So looking at table 5, this lists causes of very

high triglycerides that may be associated with pancreatitis, right?
A Yes.
Q Okay. And I highlighted a couple of these causes: Pregnancy, especially in the third trimester. Do you see that?
A Yes.
Q Can we agree that pregnancy in the third trimester is not a chronic condition?
A That's correct.
Q And certain drugs cause very high triglycerides, right?
A Yes.
Q And some of these drugs can be taken for less that 12 weeks, right?
A Yes.
Q For example, steroids?
A Yes.
Q Anything else?
A Steroids are probably the best example on this list of a drug that's often used for short term therapy, maybe Interferon as well.
Q And then diet, including alcohol, excess, we talked about that, right?
A Yes.
Q And then a high saturated fat diet?

A **Yes.**
Q **And eating high saturated fat food is not a chronic condition, right?**
A **It often is in the United States, but -- yes, it's not.**
Q **You would like to think that --**
A **It doesn't have to be.**
Q **If you tell people they'll die if they don't stop eating MacDonald's, they'll listen to you?**
A **Unfortunately not all the time, but, yes.**
Q **Okay. And diseases is up there too. As we talked about some diseases can cause severe hypertriglyceridemia if they're not controlled, right?**
A **That's correct.**
Q **And triglycerides can fluctuate based on factors such as diet and exercise, right?**
A **Yes.**
Q **And in fact a patient's triglyceride levels can vary significantly based on lifestyle and medication changes, right?**
A **Yes.**
Q **Continuing through this article, we're at DDX 3.15, and we're on page 20 of DX 1632, this slide says a weight loss of 5 to 10 percent results in a 20 percent decrease in triglycerides. That's a true statement, right, sir?**
A **Yes.**

Q **Okay. Then moving to DX 1632, page 22, DDX 3.16, the Miller reference says Mediterranean style diet versus a low fat diet is more commonly associated with an approximately 10 to 15 percent lowering of triglycerides and a reduced prevalence of hypertriglyceridemia, right?**

A **Yes.**

Q **That's true as well?**

A **Yes.**

Q **And if we go to DX 1632, pages 23 and 24, DDX 3.17, Dr. Miller says,**

> **"Ingestion of one ounce per day would correspond to a 5 to 10 percent higher triglyceride concentration than found in nondrinkers."**
>
> **Is that correct?**

A **That's an average, but, yes.**

Q **Okay. On page 24 of DX 1632, DDX 3.18, Dr. Miller says,**

> **""Optimization of nutrition-related practices can result in a marked triglyceride-lowering effect that ranges between 20 and 50 percent," right?**

A **Yes.**

Q **And on page 27 of DX 1632, which is DDX 3.19, Dr. Miller says,**

> **""Reductions of 50 percent or more in triglyceride levels may be attained through intensive therapeutic lifestyle change."**

Do you agree with that?

A **I have not seen that, but, yes, I agree.**

Q **Okay. But you understand that what Dr. Miller is saying is, he's saying no drug therapy can get you this, right? You can get this result without drugs.**

A **Yes.**

Q **And so a patient who presents with triglyceride levels of 550, for example, could eventually reduce the triglyceride levels down to 275, roughly, through intensive therapeutic lifestyle changes alone. Right?**

A **If you took a terrible patient and made them a perfect patient, yes.**

Q **Okay. But, I mean, that's going to take some time, right?**

A **But it's also not always the scenario. In your scenario to do all of these things, they have to be overweight, nonexercising, drinking person who has a terrible diet to be able to make all of those lifestyle changes, and then, in that scenario, you go from very high to high. But, yes, that is possible.**

Q **Okay. And so the mere fact that a patient presents to the doctor with triglycerides over 500 does not necessarily mean the patient requires drug therapy, right?**

A **Absolutely.**

Q **Now, Doctor, half of your patients with severe**

hypertriglyceridemia have the condition due to poor lifestyle choices, correct?

A **Let's say poor lifestyle choices contribute to the condition.**

Q **Okay. Because -- and you say that because the patients may be genetically predisposed to high triglycerides.**

A **Yes.**

Q **And, again, these lifestyle causes are not necessarily chronic, right?**

A **And I think to be accurate and consistent, I think we said a third earlier, so I would like to stay with that number if we could.**

So I don't want my -- my testimony to be changing during this transcript. We said a third of patients earlier. I think we'll stick with that number if that's okay with you.

Q **Right. We don't want your testimony to change.**

A **Right.**

Q **So you would say maybe half of your patients have poor lifestyle that has pushed the patient's triglycerides the wrong way, right?**

A **Yeah, of the people I see, probably half of them are not eating optimally when I see them, that's correct.**

Q **And that's contributing to the very high triglyceride level?**

A **Yes.**

Q **And we talked -- you talked about binge drinking, right?**
A **Yes.**
Q **Binge drinking can cause spikes in some patients above 550.**
A **Above 500, yes.**
Q **I'm sorry, above 500.**

And to be clear, and I think you made this point, you're not saying, and I think you used the example in the deposition, you're not saying at Mardi Gras everyone walking around is going to have very high triglycerides, right?
A **Very few will.**
Q **Yeah, you're saying that there are patients that are predisposed to high triglycerides, have never had very high triglycerides, but they engage in binge drinking and their triglycerides spike above 500, correct?**
A **Yes.**
Q **Okay. And these types of patients can get their triglyceride levels below 500 by cutting out the alcohol, right?**
A **If they're sufficiently close to 500, yes.**
Q **And doctors know this, right?**
A **Yes.**
Q **And so a doctor -- I mean, so a patient who presents with triglycerides let's say close to 600, and you identify at least one contributing cause as alcohol, could potentially**

benefit from taking icosapent for a short time while the patient goes off alcohol, and then could stop the treatment if it turns out the patient is now below 500 after taking out the alcohol, correct?

A I think that's completely unknown, that hypothetical. We have no idea what the short term benefits of icosapent ethyl are in terms of pancreatitis, and I think the label specifically calls that out, that the effect on pancreatitis is not known.

Q Okay. And so a doctor who sees a patient with triglycerides above 500 due to binge drinking could tell the patient stop drinking but also take Vascepa to help avoid pancreatitis, right?

A I doubt anybody would ever do that in practice, but that is a hypothetical situation.

Q And that hypothetical would be on-label, right?

A No, it would be off-label because they're not engaging in proper nutritional activity before initiating Vascepa therapy unless you think that the words saying stop drinking means that they stopped drinking.

And I can tell you that the words stop smoking do not imply that the patient has stopped smoking. So they need to engage, your label, engage in appropriate nutritional activity before initiating icosapent ethyl. I'm -- it's not my terminology. This is what you're putting forth.

Q **Okay. It would not be off-label if a patient who had triglycerides above 500 because of binge drinking, for the doctor to say, "Stop drinking, but also take Vascepa because you have a risk of pancreatitis, and we want to get your triglycerides down immediately," correct?**

A **I think that's a probably a borderline off-label use, but I would say it's appropriate to do that if their triglycerides are very, very high and the risk of acute pancreatitis is eminent.**

Q **Doctor you were deposed in it case, right?**

A **Yes.**

MR. KLEIN: You should have a copy of your deposition, but we'll play a video clip. Mr. Gross, can you play page 196, page 10 -- I'm sorry, page 196, lines 10 to 25.

(Deposition video played.)

BY MR. KLEIN:

Q **Sir, was that your testimony?**

A **Yes.**

Q **Okay. And can we agree that a patient with severe hypertriglyceridemia does not necessarily require indefinite drug therapy?**

A **Yes.**

Q **Okay. And many patients with severe hypertriglyceridemia don't require any drug therapy at all, right?**

A **That's correct.**

Q **And that's in part because weight reduction and exercise can reduce triglycerides in many patients, right?**

A **In some patients, yes.**

Q **Some patients. Okay.**

Let's take another look at the indication. We're on DX 2256, and it's DDX 3.20.

We talked about this a little bit before, but the indication is for use as an adjunct to diet, right?

A **Yes.**

Q **And adjunct in this context means in addition to diet?**

A **Yes.**

Q **And so it's pretty clear that FDA did not approve Vascepa to replace diet, right?**

A **Yes.**

Q **And the label is telling doctors that diet is the primary way to treat severe hypertriglyceridemia, right?**

A **I think that's overstating the label. Diet and Vascepa reduces triglyceride levels. I don't think it says diet alone in the label, at least I'm not aware of diet alone being the primary way to treat severe hypertriglyceridemia appearing anywhere in the label.**

Q **Doctor, I thought your testimony is that when a patient presents, you're supposed to put them on a diet first.**

A **Yes, but it doesn't usually work.**

Q **Okay.**

A **So it's not predominant way of doing it. It works in 20 percent of patients, and in 80 perfect of patients it fails. So the predominant way is to use drug therapy just to go back to the your initial question.**

Q **Right. But if you look at the indication, the indication is clearly telling doctors that they can use Vascepa as an adjunct to diet according to the doctor's discretion, right?**

A **Yes.**

Q **And in your personal practice you have seen diet and exercise alone without any drugs decrease triglyceride levels by about 25 percent, right?**

A **Yes.**

Q **And you're familiar, you talked about the MARINE study on direct, right?**

A **Yes.**

Q **Let's talk about the MARINE study, and this is DX 1694, page 24, DDX 3.21. This is already admitted.**

In MARINE, patients were given diet and exercise for a period of four to six weeks as a lead-in before the 12-week study began, right?

A **Yes.**

Q **And then, if we go to DDX 3.22 on the same page, there was then a two- to three-week qualifying period, right?**

A **Yes.**

Q **And this was to make sure that the patients who were**

going to enter the 12-week MARINE study had severe hypertriglyceridemia, right?

A **Yes.**

Q **And had severe hypertriglyceridemia that was not addressed by diet and exercise in the four- to six-week lead-in, right?**

A **Yes.**

Q **And so in this scenario, in the MARINE study, Amarin tried diet and exercise in a number of patients, and then a number of those patients didn't qualify, right?**

A **Right.**

Q **And that's because diet and exercise worked for them, correct?**

A **Yes. That's one reason. There's other reasons why people don't qualify, but, yes, that's the primary exclusion.**

Q **Okay. Fair enough.**

And then during these two to three weeks Amarin is looking at the remaining population and saying these patients qualify for the 12-week trial, right?

A **Yes.**

Q **And then we're on DDX 3.23. It's the same document, page 27, I just changed the highlighting.**

Only patients with triglycerides above 500 after this four to six-week lead-in and the two to three-week qualifying period entered into the 12-week safety and efficacy

MARINE trial, right?
A **Yes.**
Q **And, in your view, Vascepa is indicated for those patients who qualified for the MARINE study, right?**
A **Yes.**
Q **These are patients that went through some diet and exercise and still didn't get their triglycerides below 500 in that period of time, right?**
A **Exactly.**
Q **And you agree that Vascepa is indicated for those patients who qualified for the MARINE trial, right?**
A **Yes.**
Q **And defendants' labels will be directed to this patient population as well?**
A **Yes.**
Q **And all of the patients who qualified for the MARINE study could benefit from icosapent treatment, right?**
A **Potentially, yes.**
Q **And your position is that all patients who qualified for the 12-week MARINE study had severe hypertriglyceridemia, right?**
A **Yes, at baseline visit.**
Q **Now, Doctor, some of the patients that qualified for the MARINE study were put into a placebo group, right?**
A **Yes.**

Q **Okay. And all of the patients in the placebo group had triglycerides above 500.**

A **Yes.**

Q **Okay. And let me change documents. This is DX 1701, page 51. This is from the medical review. Do you remember looking at that?**

A **I've seen it. I didn't review it in great detail, but, yes, I've seen this document.**

Q **You used this on your direct examination, right, the FDA medical review?**

A **I think I referenced one section of it, but, yes.**

Q **Okay. And for the record this is DDX 3.24.**

The subjects in the placebo group in MARINE were instructed to maintain the diet and exercise regimen throughout the entire 12-week period, right?

A **Yes.**

Q **And those -- so those patients in the placebo group didn't get any Vascepa.**

A **That's correct.**

Q **And after 12 weeks of continuing a diet and exercise regimen, 21 percent of those subjects in the placebo group, 16 out of 75, were able to achieve and maintain triglyceride levels below 500 milligrams per deciliter by the study endpoint, correct?**

A **Yes.**

Q **And that's the green bar on DDX 3.24, right?**
A **Yes.**
Q **And so according to MARINE, about 21 percent of patients falling within the scope of defendants' indication can achieve and maintain triglyceride levels below 500 with diet and exercise alone, correct?**
A **Yes.**
Q **And these patients didn't need any Vascepa to get below 500, right?**
A **That's correct.**
Q **And these patients could benefit from a short course of icosapent given that they qualified for the MARINE study, but long-term they wouldn't require Vascepa to maintain levels below 500, right?**
A **How would they benefit? I don't understand the question.**
Q **Well, these are patients who, in the first four to six weeks tried diet and exercise alone and it didn't work, right?**
A **Right.**
Q **Okay. And so if these patients in the placebo group were given Vascepa immediately, their triglyceride levels would drop more quickly, right?**
A **Probably, yes.**
Q **And by the time you get into the 12-week period, they wouldn't even need Vascepa, according to MARINE, to maintain**

levels above 500, right?
A You're talking about those 21 percent.
Q Correct.
A Yes.
Q And consistent with MARINE, about 20 percent of your patients with severe hypertriglyceridemia are able to reduce their triglyceride levels below 500 with diet and exercise alone, right?
A Yes.
Q And so about one-fifth or 20 percent of patients with very high triglyceride levels don't necessarily need any drug therapy to get their levels below 500, right?
A That's correct.
Q Now, even in those patients who don't necessarily need Vascepa, you still sometimes prescribe Vascepa, right?
A I would never prescribe a drug that I don't perceive they need, no.
Q Well, you -- well, let's come back to that.

Now, some of your patients who were able to reduce triglycerides below 500 with diet and exercise alone say no thanks when you suggest Vascepa, right?
A Right. They can't get it or they don't want to take it. That's correct.
Q And this happens with some frequency because you have a lot of patients who don't like taking drugs unless they need

to, right?
A Yes.
Q You practice in California so you may see that more often than others.
A Yes.
Q Okay. And the dosing regimen for Vascepa is four pills a day twice a day.
A Four pills a day total; two twice a day.
Q That's what I meant. I'm sorry. Two pills in the morning and two in the evening, right?
A Yes.
Q That's an inconvenient dosing regimen for many patients, right?
A Yes.
Q And so you have patients who start on Vascepa therapy and then stop.
A Yes.
Q About ten percent of your patients stop taking Vascepa for various reasons, right?
A Yes.
Q And you agree that patients could follow the Vascepa labeling and effectively treat patients with severe hypertriglyceridemia for less than 12 weeks, right?
A Can you say that again? I'm sorry.
Q Okay. You agree that physicians could follow the Vascepa

labeling and treat severely hypertriglyceridemic patients with Vascepa 4 grams per day for fewer than 12 weeks and achieve an effect, correct?

A Yes.

Q Okay. In other words, Vascepa is suitable to reduce triglyceride levels in patients suffering from severe hypertriglyceridemia in less that 12 weeks, right?

A Yes.

Q And, in fact, some patients with severe hypertriglyceridemia taking icosapent because they don't need to -- let me stop and rephrase.

Some patients with severe hypertriglyceridemia stopped taking icosapent because they don't need to take the drug long-term to keep triglycerides below 500, correct?

A I think that's a minority, but, yes.

Q Okay. And after all, icosapent can significantly reduce triglycerides in as few as four weeks, maybe even sooner, right?

A Yeah, I don't think anybody knows sooner, but we have data at four weeks.

Q Right. The first data point was four weeks, it could be sooner, we don't know, right?

A Yeah, I don't think anybody knows that.

Q And let's go to DX 3.26 which is DX 1694, page 214. You recognize this as the MARINE study?

A **Yes.**
Q **And MARINE reported the most significant reduction in triglyceride levels at just four weeks, right?**
A **Yes.**
Q **And on the screen, just so, you know, everyone is oriented, the baseline median triglyceride was about 680, right?**
A **Yes.**
Q **And then by week four, the median triglyceride dropped to 471, right?**
A **Yes.**
Q **And so by week four, the median patient had a triglyceride level below 500, right?**
A **Yes.**
Q **Let's go to the next document which is DX 1816, page 70, and it's DDX 3.27. I will represent to you that this is a document that's already been admitted from Amarin to the FDA.**

And it says -- this portion of the document says,

"Time course of effects: In studies in which serial measurements were performed and/or reported, the maximum effect was seen at four to w 8 weeks, after which time the reduction was maintained."

Are you familiar with that?

A **Yes.**
Q **Okay. And that's an accurate statement, right?**

A **Yes.**
Q **And so icosapent works well if a doctor wants a drug to get triglyceride levels below 500 quickly to eliminate the risk of pancreatitis, right?**
A **To reduce the risk of pancreatitis, yes.**
Q **Fair. Fair point.**
Okay. So if you assume a patient who has just barely above 500, let's say 510, and the patient can reduce their triglyceride level by 25 percent with diet and exercise eventually, like the -- like the placebo patients in MARINE, a doctor reasonably could prescribe icosapent for short-term use to reduce the pancreatitis risk as soon as possible, right?
A **So -- yes, they could do that.**
Q **And some of your patients start Vascepa after testing above 500, and then think they don't need the drug anymore once their levels drop below 500, right?**
A **There are some patients who do that, yes.**
Q **In fact, about 5 percent of your patients stopped taking Vascepa after they see their triglycerides drop below 500, right?**
A **Yes.**
Q **And this drop below 500 can happen in less than 12 weeks on icosapent, right?**
A **Theoretically, yes. I don't measure it at less than 12 weeks, but, yes.**

Q **Okay. And in your personal practice, some of your patients do take -- strike that.**

In your -- in your practice, some of your patients with very high triglycerides take Vascepa for less than 12 weeks, right?

A **Yes.**

Q **And when they stop Vascepa, you don't feel that their lives are being put at risk given the pancreatitis risk, right?**

A **The moment they stop? No.**

Q **Okay. And about 5 percent of your patients with severe hypertriglyceridemia take Vascepa for less than 12 weeks, correct?**

A **Yes, for various reasons.**

Q **Now, we've touched on this earlier, but certain drugs can cause triglyceride levels to spike, right?**

A **Yes.**

Q **And we talk about -- we talked about steroids or corticosteroids as an example, right?**

A **Yes.**

Q **And I believe you said corticosteroids can be used short term, right?**

A **They most often are.**

Q **Yeah, less than 12 weeks?**

A **Yes.**

Q **Okay. And a patient who needs a short-term corticosteroid treatment could take Vascepa to counteract the side effect of the triglyceride level spike if necessary to address, right?**

A **Again, a very unusual hypothetical, but I guess that's theoretically possible.**

Q **Now, let's go to DX 2256, page 7, which is DDX 3.28 and you recognize this as the clinical study section of -- this is Hikma's label, but the identical language is in DRL's label, right?**

A **Yes.**

Q **And the clinical study section summarizes the study that justified the FDA approved indication, right?**

A **Yes.**

Q **We know that it's a MARINE study, but the label doesn't actually identify the study name, right?**

A **Correct.**

Q **And the clinical study section provides data beyond the scope of the indication, right?**

A **Yes.**

Q **And some of the data may be relevant to a prescribing physician, right?**

A **Yes.**

Q **But some of the data may be completely irrelevant to a prescribing physician, right?**

A **Yes.**
Q **In other words, some physicians will find some of the clinical study information helpful, but others will find it irrelevant to their practices, right?**
A **Yes.**
Q **And the clinical study section says the study supporting the indication lasted 12 weeks. We talked about earlier, right?**
A **Yes.**
Q **The study certainly didn't last more than a year, right?**
A **That's correct.**
Q **The study ended at 12 weeks, right?**
A **There was the -- the carry-on up to a year.**
Q **For -- right, for some patients.**
A **Yes.**
Q **Okay. And this section -- and we talked about this earlier. This section, the clinical study section, does not specifically instruct doctors that in view of the 12-week clinical study, doctors should go ahead and make sure they give icosapent for at least 12 weeks, right?**
A **Encourages them to use it for at least 12 weeks to see what the effects will be, to see if they achieve the effects in table 2.**
Q **Okay. You're talking about some kind of implied encouragement, right?**

A **I don't want to get into legal terms. I think it encourages physicians to try to follow the clinical study to see if it happens in their patients.**

Q **And just to be clear, I wasn't asking you a legal question. The only time the term 12 weeks is used in defendants' label is to describe the underlying clinical trial, right?**

A **Yes.**

Q **In other words, defendants' labels don't otherwise comment on the 12-week duration such as saying because these effects were achieved in 12 weeks, make sure you give the drug for at least 12 weeks. There's nothing like that, right?**

A **It doesn't say that explicitly, that's correct.**

Q **Let's take a look at the patient information, DX 2256, page 9, which is DDX 3.29. You talked about this on direct, right?**

A **Yes.**

Q **Okay. And the second bullet says,**

> **"Do not change your dose or stop taking icosapent ethyl without talking to your doctor," right?**

A **Yep.**

Q **This statement is it not instructing doctors and patients so use icosapent for at least 12 weeks, right?**

A **Correct.**

Q In fact, this statement doesn't speak to whether the label is encouraging any particular duration, right?
A Right. The statement just warns them if you're going to stop it, talk to your doctor.
Q Now, even if one of your patients does not necessarily need icosapent long-term, you still often prescribe it long-term, right?
Let me rephrase the question because now there are two indications.
Even if your patient with severe hypertriglyceridemia does not necessarily need icosapent long term to address the severe hypertriglyceridemia, you still prescribe the drug long-term, right?
A My intent is, when I'm treating people with Vascepa for severe hypertriglyceridemia, that they're going to need the drug long-term, and my intent is to give it to them long-term.
Q But you also give your patients Vascepa long-term for reasons unrelated to severe hypertriglyceridemia, right?
A Can you say that again? I'm sorry.
Q You prescribe Vascepa to your patients for reasons unrelated to controlling severe hypertriglyceridemia.
A You're talking about the other indication.
Q Right.
A I thought we weren't going it talk about the REDUCE-IT indication.

Q **Well, I'm not going it talk about the specific indication, I'm talking about your practice.**

A **Which addresses the second indication, yes. I use it for the REDUCE-IT indication.**

Q **Okay. And before the new indication was approved, you often prescribed Vascepa for reasons unrelated to controlling severe hypertriglyceridemia, right?**

A **I used it for that same purpose, for the REDUCE-IT type indication, for the REDUCE-IT study results, to try to emulate that in my practice, yes.**

Q **And you also used it because you're not satisfied when your patients have high triglyceride levels. You want it lower, right?**

A **So I would sometimes use it when they were close to 500 and not exactly 500, but that would probably be considered an off-label use.**

Q **Right. And before the new indication was approved, you often prescribed Vascepa for off-label uses, right?**

A **Yes.**

Q **And did you that because you thought that could help address cardiovascular issues, right?**

A **Because I knew the results of REDUCE-IT, the study, I was an investigator, and I wanted to emulate that in my patients.**

So, yes, there was a window where before REDUCE-IT indication came out, but after the REDUCE-IT trial came out,

that I was informed that that's a really good idea to treat those patients to reduce their cardiovascular risk, and I started doing that, and the guidelines encouraged me, but the FDA did not opine on that until December 2019.

So there was a window where I was using it for REDUCE-IT, but the indication was not yet in the label.

Q Right. And just to be clear, doctors are allowed to prescribe drugs off-label, correct?

A Yes.

Q So I'm certainly not suggesting you're doing anything wrong. You understand that.

A No, I just want to explain why my off-label use.

Q Yeah. And so you had patients who had -- who may have presented with triglycerides at, say, 550, who you thought maybe were overweight and weren't in shape and could probably maintain levels below 500 without Vascepa, you told them continue taking the drug because it might have additional benefits, right?

A Yeah. Especially after the REDUCE-IT trial, yes.

Q Okay. And icosapent is fairly well tolerated, right?

A Yes.

Q So there's not too much of a downside if your patient is tolerating the medication, and they don't necessarily need it for severe hypertriglyceridemia, to tell them to continue the medication because there may be cardiovascular benefits,

right?
A That's a given indication now as well, yes.
Q Right. And even -- you have -- even before the new indication, you used Vascepa to treat triglyceride levels to get them down as low as 135, right?
A I never targeted 135, but some patients might have gotten to 135.

135 is the entry criteria for the REDUCE-IT trial. That's not a goal or target. That was -- that just happened to be a random number that was -- that was started at with the study, but the targets are less than 150, not 135.
Q I see. But you routinely, before and now after the new indication, have been prescribing Vascepa often to address triglyceride levels that are not above 500 but are still too high, fair?
A Yes, the REDUCE-IT indication.
Q And you understand that defendants' products will not be indicated for cardiovascular effects, right?
A Yes.
Q And so even before the new Vascepa indication, about 85 percent of your prescriptions were off-label, right?
A Again, I just explained why. But, yes, that was the window between the REDUCE-IT results being published and the REDUCE-IT indication being changed by the FDA. At that point I was using it for the REDUCE-IT indication that was not yet

part of the label.
Q Okay. And just to be more clear, that 85 percent of your patients did not ever have triglycerides above 500, correct?
A That -- right, correct.
Q Okay. And now that there's a new indication, do you expect the percentage of prescriptions that would be off-label to defendants' labels to be higher than 85 percent?
A I think it would be very high. I don't know if it will be higher or lower than 85 percent.
MR. KLEIN: Mr. Gross, can you turn to PX 277.
BY MR. KLEIN:
Q Let's start with the first page. Do you remember this exhibit from the Jacobson reference that you discussed on direct examination?
A Yes.
Q Okay. I just a couple questions about this.
Let's go to page 26, and do you remember discussing this section of the article on follow-up visits?
A Yes.
Q Okay. And just to be clear, this article in the discussion you were focusing on was talking about statins, right?
A This paragraph was talking about statins, yes.
Q Right. And if we back out of this and go the page before, which is PX 277, page 25, that section that you were

discussing is under a larger header -- heading called Cholesterol Lowering Drug Therapies, right?

A Yes.

Q Not very high triglycerides, right?

A Yes.

MR. KLEIN: All right. Let's go back -- can you go back to the PowerPoint.

BY MR. KLEIN:

Q Let's go back to DDX 3.30. This is again back to the indication. And now you're aware of certain asserted patent claims, and you just discussed them on direct, that focused on lipids other than triglycerides, right?

A Yes.

Q Now, defendants' labels will be indicated solely to reduce triglycerides in the specific population, right?

A Yes.

Q And you understand that defendants' labels will not be indicated to reduce any lipid parameter other than triglycerides, right?

A Correct.

Q And so a doctor could follow the indication in defendants' labels and prescribe their products, once they're introduced, to reduce triglycerides and not focus on any other lipid parameters, right?

A They don't have to focus on other parameters, that's

correct.
Q Let's go to DDX 3.31, we're in DX 2256, pages seven to eight. This is table 2 of defendants' label.
I assume this is familiar, right?
A Yes.
Q And there's a statement underneath the table that you talked about on direct, right?
A Yep.
Q And that statement is reporting on observations concerning the clinical trial that's being reported in table 2, right?
A Yes.
Q And these are not instructions on how to use icosapent, right?
A Correct.
Q They're mere descriptions of the clinical study results.
A No, they're to show you what to expect if you use the drug.
Q Okay. And they're describing the clinical study results, right?
A Yes.
Q Okay. And, in your opinion, doctors will see the phrase icosapent 4 grams per day, reduce median triglyceride, VLDL-C and apo B levels from baseline relative to placebo and infer an instruction that doctors can expect similar results in a

majority of individual patients, right?
A Yes.
Q And that inference goes beyond the scope of the indication, right?
A Of the specific indication? Yes.
Q Yes. And median data from a clinical trial may or may not relate to an individual patient depending on, for example, the specific patient population that was being tested, right?
A Yes.
Q And, for example, the information in the clinical study section says that the median triglyceride level was 684, right?
A Yes.
Q Okay. And a doctor would understand that the effects listed in table 2 may not be the same if the patient's triglyceride levels were, for example, only 500, right?
A As long as they're above 500, they should have these general results.
Q Okay. Or a patient with 2,000, with triglycerides of 2,000, may or may not receive these -- obtaining those same results, right?
A I think patients in this trial with triglycerides above 750 did a little better.
Q Now, the label, defendants' labels are not encouraging doctors to use Vascepa to obtain effects unrelated to

triglycerides, right?
A I'm sorry, could you say that again?
Q Let me rephrase. Defendants' products are not indicated to control LDL-C, right?
A That's correct.
Q Okay. And you don't prescribe Vascepa to avoid raising LDL-C, right?
A No, that is one of the considerations of why I choose Vascepa over other generics.
Q Fair enough. But your intent in prescribing icosapent is to lower triglyceride levels, not to effect LDL-C levels, right?
A It's to lower triglyceride levels without raising LDL-C.
Q Well, defendants' labels are not encouraging doctors to use the drug because it controls LDL-C, right?
A That's correct.
Q Let's take another look at table 2 again, it's DX 2256, pages 7 to 8, DDX 3.32, and I want to focus now on the LDL-C results, do you see that?
A Yes.
Q Now, the doctor would understand from table 2 and the statement below it that we looked at, that there was no LDL-C increase for an average patient, right?
A That's true.
Q Okay. And there are footnotes that denote the

statistical significance, you talked about that, right?

A **Yes.**

Q **And the LDL-C data does not reference either of the two footnotes, right?**

A **Correct.**

Q **And so a doctor reading defendants' label would understand that the LDL-C data in table 2 is not statistically significant, right?**

A **Correct.**

Q **And there's a column marked Difference (95 Percent Confidence Level), do you see that?**

A **Yes.**

Q **There are two numbers in the parenthesis for the LDL-C, minus 13 and plus eight, right?**

A **Yes.**

Q **And the plus eight means that within the group representing 95 percent of the patients in the study, LDL-C increased as high as eight percent, right?**

A **Yes.**

Q **And that would be a clinically meaningful increase, right?**

A **Yes.**

Q **And the doctor -- so the doctor reading defendants' label would understand that some percentage of patients in this study actually had an LDL-C increase, right?**

A **There will be some, yes. There are outliers to any effect.**

Q **And based on this information in defendants' labels, a doctor would understand that some patients taking icosapent will actually experience a clinically significant LDL-C increase, right?**

A **That is possible, and that's why we repeat the lab values at 12 weeks to see if anything has happened.**

Q **Okay. Let's go to the next slide which is DDX 3.33. We're looking at DX 2256, page 8, which is Hikma's proposed label, and DX 1578 which is the Lovaza label. Both documents are in evidence.**

You recognize these two documents, right?

A **Yes.**

Q **And you talked about the Lovaza warning, right?**

A **Yes.**

Q **Okay. And your opinion is that doctors will compare the top snapshot from defendants' labels to the Lovaza warning about LDL-C, right?**

A **Yes.**

MR. KLEIN: Okay. Actually, it's the Lovaza warning -- that's in evidence, right?

Let me move just in case, the Lovaza label may be a PX so let me move to admit DX 1578 just in case it's not in evidence.

MR. M. KENNEDY: No objection, Your Honor.

THE COURT: It hasn't been admitted. DX 1578 is admitted.

(Defendants' Exhibit 1578 received in evidence.)

BY MR. KLEIN:

Q **And so your opinion with regard to the LDL-C limitation assumes that the doctor reading defendants' label would be aware of this warning in the Lovaza label, right?**

A **Yes.**

Q **And it's your opinion that -- and your opinion assumes that the doctor would compare the adverse reactions from the Lovaza study to the -- Hikma's proposed label and the study in Hikma's label, right?**

A **Yes.**

Q **Okay. And this LDL-C statement in Hikma's label would carry significance to a doctor only because and if the doctor understood that Lovaza had this side effect, right?**

A **Yes.**

Q **Otherwise, it wouldn't mean much to the doctor to say there was no LDL-C increase, right?**

A **Correct.**

Q **Defendants' labels never tell doctors to compare the icosapent clinical trial to the Lovaza clinical trial, right?**

A **Correct.**

Q **And, in fact, defendants' labels don't refer to the**

Lovaza label at all, right?

A **Correct.**

Q **Let's go to DDX 3.34 which is DX 2256, page 3. This is section 6.1 of Hikma's propose label. You've seen this, right?**

A **Yes.**

Q **And this section is called Clinical Trials Experience, and it says,**

> **"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice," right?**

A **Yes.**

Q **In other words, defendants' labels is telling doctors and warning them against comparing adverse reactions from two clinical trials involving 2 different drugs, right?**

A **Yes.**

Q **So this warning section, 6.1 in defendants' labels, would cover comparing the Vascepa LDL-C adverse reaction rates with the Lovaza LDL-C adverse reaction rates which was obviously a separate trial, right?**

A **Well, the LDL rates are part of the primary study. Adverse reactions are usually side effects like bleeding or**

joint pain or back pain or rash. So these are a little bit different.

Q But a doctor would understand reading -- a doctor reading defendants' labels would understand that two clinical trials involving two different drugs are conducted under different situations, and they may or may not be comparable, right?

A Yes.

Q And a doctor reading defendants' labels as a whole would obviously see section 6.1, right?

A Yes.

Q Now, you -- on direct you talked about how some asserted claims require reductions in apo B. Do you remember that?

A Yes.

Q Let's take another look at Hikma's label DX 2256, page 8, DDX 3.35. And this -- you talked about this statement on direct, "icosapent ethyl 4 grams per day reduced," and I'm just going to focus on "apo B levels from baseline relative to placebo." Do you remember that?

A Yes.

Q Now, this statement would not necessarily affect prescription decisions, right?

A It could because apo B going down would lower cardiovascular risk, and, again, that's an indication for Vascepa.

I realize it's not in your label, but we already

talked about people potentially using your product off-label to get that benefit. So I think is this the benefit REDUCE-IT, is that Vascepa or icosapent ethyl lowers apo B, therefore lowers cardiovascular risk.

So I think this is a very important point that doctors would use the drug for to achieve cardiovascular benefit.

Q Okay. And those cardiovascular benefits would be beyond the scope of defendants' labels, right?

A Yes.

Q Now, on direct you told the Court that you prescribed Vascepa with the intent to reduce apo B; is that right?

A Yes.

Q But you don't focus on apo B in your practice, right?

A I don't often measure it, no.

Q You often don't even look at apo B, right?

A If it's available, I look at it, but I don't send patients to the lab for apo B measurements routinely.

Q And so when you prescribed Vascepa, reducing apo B is not an intended result with regard to treating severe hypertriglyceridemia, right?

A No, it's more for cardiovascular risk as I stated.

Q And defendants' products are not indicated specifically to reduce triglycerides by any particular amount, right?

A That's correct.

Q And it would be consistent with the Vascepa labeling to prescribe the drug to patients with severe hypertriglyceridemia even if you only wanted to have a 5 percent reduction, right?

A I don't think that would be the intent of the physician, but if that occurred, that would still be an on-label use.

Q Now, let's take a look at DDX 3.36, and this is DX 2256, page 21. Do you recognize this as claim 1 of the '728 Patent?

A Yes.

Q And I highlighted the limitation "who does not receive concurrent lipid-altering therapy." Do you see that?

A Yes.

Q And on direct you testified that a statin is an example of a lipid-altering therapy, right?

A Yes.

Q Probably the most common example, right?

A Yes.

Q But there are other lipid-altering therapies, right?

A Yes.

Q For example, fibrates, niacin, right?

A Yes.

Q And also Zetia; is that right?

A Yes.

Q And the chemical name is Ezetimibe?

A Yes.

Q **And in your practice, your patients very commonly take Vascepa with a statin, right?**
A **Yes.**
Q **And you don't read the Vascepa labeling as requiring doctors and yourself to give the drug without a statin, right?**
A **It's -- right. You have the option as a physician to use it with or without a statin.**
Q **For example, you don't -- in your practice, you wouldn't start Vascepa with no statin, wait for the triglycerides to decline below 500, and then add a statin later, right?**
A **I may. I gave an example of that during my direct.**
Q **Okay. But that's not the common way you would use Vascepa, right?**
A **It's more commonly patients are already on a statin and their triglycerides are above 500, so I might implement Vascepa.**
Q **And maintain the statin therapy, right?**
A **Yes.**
Q **And if we go to DDX 3.37, this is DX 2256, page 7, this is the portion of defendants' label that says 25 percent of patients were on concomitant statin therapy, right?**
A **Yes.**
Q **And this is just letting doctors know that 25 percent of patients in the clinical study discussed in the labeling were taking a statin, right?**

A **Yes.**
Q **In other words, this sentence is just -- or this phrase is just discussing the study protocol, right?**
A **Yes.**
Q **This sentence is not an instruction to doctors to make sure they use a statin, right?**
A **It's not a mandate to use a statin in this indication.**
Q **And it's not mandating not to use a statin either.**
A **Right.**
Q **Okay. And this statement doesn't say anything about other lipid-altering therapies, right?**
A **Correct.**
Q **And so the statement is not requiring doctors and patients to take icosapent without any concurrent lipid-altering therapy, right?**
A **It's not forcing them, right. They can use it as monotherapy, it's indicated as monotherapy, but it's not mandated as monotherapy.**
Q **And when you read this phrase, you inferred that 75 percent were not on a statin, right?**
A **Yes.**
Q **Okay. But the labeling doesn't say anything about whether this 75 percent of patients were taking a different lipid-altering therapy, right?**
A **Right. We know most of them were not.**

Q **But you know from the MARINE study.**
A **Well, that's what this is referring to, yes.**
Q **No, but if a doctor were just reading the label, the doctor couldn't tell whether those 75 percent of patients were on a different lipid-altering therapy correct?**
A **Right.**
Q **And even if we just focus on statins, there's nothing in the clinical trial section or the label as a whole suggesting any preference for using icosapent with or without a statin, right?**
A **I think it encourages the option of either, but it doesn't say you have to use it one way or the other for that indication.**
Q **And, in fact, a doctor would not even be able to infer a preference with or without a statin from what's in the label, right?**
A **Well, I think, again, it's up to the clinical judgment of the physician and the clinical scenario of patient, and that is left to the doctor, the treating doctor, as we described before.**
Q **Right. So the defendants' labeling leaves it entirely up to the physician's discretion as to whether to add a concurrent lipid-altering therapy to icosapent, correct?**
A **Right. If it's needed you add it, if it's not needed, you don't have to add it.**

Q **All right. Now --**

THE COURT: Mr. Klein, are you transitioning --

MR. KLEIN: I am.

THE COURT: -- to another exhibit?

I think it would make sense to take our afternoon recess at this time.

We'll take a 15-minute recess.

(A recess was taken.)

THE COURT: Please be seated.

Mr. Klein, are you ready?

MR. KLEIN: Thank you.

BY MR. KLEIN:

Q **Dr. Budoff, you're not a lawyer, right?**

A **No.**

Q **And you're not an expert in patent law, right?**

A **No.**

Q **And I noticed, for the large part, you avoided any type of legal conclusions, right?**

A **I tried.**

Q **Okay. You're certainly not offering any opinions as to the legal standards for patent infringement, right?**

A **Correct.**

Q **And you're not testifying about whether any language in defendants' proposed labeling actually meets specific legal standards, correct?**

A **Correct.**
Q **You weren't familiar with the legal standards for patent infringement before this case, right?**
A **No.**
Q **And the legal standards for induced infringement can be a bit confusing? Did you find them confusing?**
A **Yes.**
Q **Okay. You're not the only one.**
But do you understand that you might consider a particular statement in the labeling to encourage infringement, but the case law might require more specific statements to induce, right?
A **Yes.**
Q **And your understanding when preparing your reports was that a product label induces infringement if the doctor follows the label and ends up using the drug on-label for an infringing use, right?**
A **Yes.**
Q **And on your direct, let's go to DDX 3.38, which is a copy of PDX 2-10, you talked about the legal standards that you applied, right?**
A **Yes.**
Q **And in the second bullet, you said,**
"Evidence that defendants' labels would inevitably lead some clinicians to infringe

establishes defendants' intent to induce infringement," right?
A Yes.
Q And that came from the lawyers, presumably, right?
A Yes.
Q And -- but your view in preparing your reports was that at least -- if at least some physicians will prescribe Vascepa or its generic equivalent for severe hypertriglyceridemia to lower triglycerides, that means the label inevitably induces infringement, right?
A Yes.
Q And you understand that that phrase actually comes from case law?
A Yes.
Q And you're not offering an opinion on whether that particular phrase as construed by the courts has been satisfied by the labels, right?
A Leave that to the Court.
Q Exactly.
Now, Dr. Budoff, you have a long consulting history with Amarin outside the context of this case, right?
A Yes.
Q And, for example, Amarin has retained you as a Thought Leader to discuss the Vascepa product?
A Yes.

Q **And you also served on Amarin's Speakers Bureau for Vascepa, right?**

A **Yes.**

Q **Let's go to the next slide, which is DX 2003, and it's DDX 1.39. Did you see this document during opening statements?**

A **Yes.**

Q **Is this a document you've seen before?**

A **No.**

MR. KLEIN: Okay. I move into evidence DX 2003 as an Amarin document.

MR. M. KENNEDY: No objection, Your Honor.

THE COURT: 2003 is admitted.

(Defendants' Exhibit 2003 received in evidence.)

BY MR. KLEIN:

Q **This -- you were on, and still are, actually, on Amarin's Speakers Bureau, right?**

A **Yes.**

Q **Okay. And this -- this document says, "Dear VITAL Speakers." Do you understand VITAL is an abbreviation for advanced -- to Advance Interventions and Total Assessment of lipids?**

A **Yes.**

Q **Do you know what that is?**

A **That's just the name of their Speakers Bureau.**

Q **I see. Okay.**

And that's -- the Dr. Matthew Budoff is you on this page, right?

A **Yes.**

Q **And you recognize Dr. Toth as well?**

A **Yes.**

Q **And you recognize Dr. Mason?**

A **Yes.**

Q **Do you understand he, along with yourself and Dr. Toth, are all experts for Amarin in this case?**

A **Yes.**

Q **And if we go to DDX 3.40, there's a picture of Dr. Miller, right?**

A **Yes.**

Q **Is that the doctor who wrote the publication we looked at earlier?**

A **Yes.**

Q **Okay. And you understand now that he was actually retained as another Amarin expert earlier in the case?**

A **You told me that, yes.**

Q **Yeah.**

And you began consulting for Amarin about eight years ago, in 2012?

A **Yeah. I'd have -- I don't know exactly, but somewhere around that time.**

Q **Okay. And with regard to Amarin's Speakers Bureau, you encourage clinicians to use Vascepa, right?**

A **No, I try to educate them on the science and the guidelines. It's not my job, nor would I ever encourage them to use a specific product outside of what would be appropriate and best for the patient's care.**

Q **Okay. Understood. But Amarin was paying you to go out and speak to doctors about Vascepa, right?**

A **Yes. I get paid by a lot of different groups to give lectures. It's on my own time. I have to travel. So I do get compensated when I have to lecture most of the time.**

Q **You served as an Amarin speaker for Vascepa about a 100 times; is that right?**

A **I wouldn't know exactly, but it's possible over the seven years.**

Q **You estimate maybe 100 in your deposition. Does that sound right?**

A **Yeah.**

Q **And I think you've said this earlier, you're still a speaker for Vascepa today, right?**

A **Yes.**

Q **And as an Amarin Thought Leader, you gave Amarin advice on how to help market Vascepa to physicians, right?**

A **Not generally. I usually give them advice on what science to do or what next study to do.**

I've met with them about the EVAPORATE trial and tried to encourage them to do other studies. I'm not a marketing expert, so I don't give them marketing advice.

Q You gave Amarin general advice or direction on what things about Amarin's clinical study may resonate with clinicians or what things should be emphasized or de-emphasized; is this right?

A Yes.

Q And you also consulted with Amarin on the REDUCE-IT trial? You talked about that, right?

A Yeah. I wasn't directly involved in the REDUCE-IT trial, outside of being a principal investigator. I wasn't on the steering committee or anything. So, I wasn't really involved in that other than recruiting some patients locally at my own site.

Q Okay. And just to be clear, REDUCE-IT focused on a different patient population than the patient population we're talking about in defendants' labels, right?

A Yes.

Q And you also sent proposals to Amarin with regard to the EVAPORATE trial, right?

A Yes.

Q And since 2016, about half of your income comes from pharmaceutical companies, including Amarin, right?

A All lectures combined, but, yes.

Q **And about 10 percent of your income comes from Amarin, right?**

A **Yeah.**

Q **And you also testified for Amarin at the FDA Advisory Committee meeting held last November for the new REDUCE-IT indication, right?**

A **I was just a public speaker. That was on my own behalf.**

MR. KLEIN: Okay. Let's go to DX 2246, pages 1 and 62, and it's DDX 3.41. This is Amarin's supplemental NDA financial disclosure.

We'll move this into evidence.

MR. M. KENNEDY: No objection, Your Honor.

THE COURT: 2246 is admitted.

(Defendants' Exhibit 2246 received in evidence.)

BY MR. KLEIN:

Q **I don't know, have you seen Amarin's financial disclosure with regard to its supplemental NDA?**

A **No.**

Q **Okay. I'll represent to you that that's what this is.**

You know what the financial disclosure is, right?

A **Yes.**

Q **And Amarin had to make financial disclosures to the FDA for you and other investigators, right?**

A **Yes.**

Q **Okay. And Amarin submitted this document on March -- in**

March 2019, right? You see that at the bottom?
A Yes.
Q Okay. If we turn to Section 3, it's DX 2246, page 3, DDX 3.42, the document -- you see the title, Clinical Investigators With Disclosable Interests?
A Yes.
Q And the document explains that,

"Clinical investigators with disclosable financial interests including a significant equity interest in the sponsor of the covered study as defined in" the regulations "and/or significant payments of other sorts (SPOOS)," S-P-O-O-S, "as defined" in the regulations, "are provided in Table 1. Details of their disclosed financial interests and arrangements are included in Table 2."

Do you see that?
A Yes.
Q All right. Now, let's go to the next slide DX 2246, pages 3 to 4. This is DDX 3.43. You see this is Table 1?
A Yes.
Q And can you see that you are one of the doctors who was disclosed by Amarin?
A Yes.
Q And if my count's right, there were 12 in total.
A Okay.

Q **All right. Now, turning to the next page, DX 2246, page 7, this is DDX 3.44, Table 2 lists the details of the disclosed financial interests and arrangements for the 12 people we just looked at. Do you understand that?**

A **Yes.**

Q **Okay. And, again, this -- you are the Matthew Budoff on the left there?**

A **Yes.**

Q **And Table 2 lists SPOOS, which was defined earlier as Significant Payments of Other Source -- Sorts, for you of close to $1.3 million. Do you see that?**

A **Yes.**

Q **And then the table breaks this down. Do you see that?**

A **Yes.**

Q **And so Amarin has provided you with a research grant of $900,000 related to the EVAPORATE study, right?**

A **That goes to my institution, not to me, but, yes.**

Q **And just so you know, my next question was, to be fair, you didn't receive the money personally.**

A **Right.**

Q **Okay. But it does help a study that you proposed to Amarin, right?**

A **Yes.**

Q **And you're the principal investigator for that study.**

A **Yes.**

Q **And your name will be associated with the results of the study if it's successful, right?**

A **It already is. I've been publishing on that trial.**

Q **We go to the next slide, it's the same page, different highlighting, DDX 3.45, you received a higher research grant than any of the other 11 individuals listed in the table, right?**

A **Yes.**

Q **Now, if we go to the next slide, which is DDX 3.46, again, it's the same slide, I just changed the highlighting. If we take out the $900,000 grant, the rest of the $1.3 million was paid by Amarin to you personally, right?**

A **No. The honorarium and consulting fees goes to me personally. A lot of the compensation might go to my institution. For example, I do educational programs at my institution, and they support that. That money would go to the institution and not to me.**

Q **Okay. But it's your institution, correct?**

A **No, I don't own it. It's named the Lundquist Institute. I'm one of 1,000 investigators there, and the money that goes to the institute supports all of our services there; research, pharmacies, the statistics, a lot of different things.**

Q **Okay.**

A **It doesn't benefit me personally in any way.**

Q **Well, it benefits you personally indirectly to the extent**

it's benefitting an institution to which you belong, correct?
A Well, yes, but they just received a $70 million grant to name the institution, so my contribution of a total of 300,000 is probably not very significant, and that money doesn't go to me as well.

So I would say that I'm definitely responsible for receiving the consulting fees of 33,000 and the honorarium of 27,000. I don't know what education of $42 represents, but let's -- I'll take credit for that as well, maybe I received that payment.

Q Okay. Over the years, for your consulting work, unrelated to this case, you would guess you have received probably $300,000, or something over, spanning the last eight years, right?

A No, nowhere near that number.

Q Okay.

A That would be listed here if that were the case.

MR. KLEIN: Mr. Gross, can you play the 272 -- page 272 of his deposition, line 24, to 273, line 6.

(Deposition video played.)

BY MR. KLEIN:

Q Doctor, was that your testimony?

A Yes, but that includes money that goes to my institution, not to me personally.

Q The question -- okay.

A **I apologize. I didn't understand your question.**

Yes. It says right here, 302,000. I think that number is probably very accurate.

MR KLEIN: No further questions.

MR. M. KENNEDY: Your Honor, I do have a little bit of redirect.

Your Honor, may I proceed?

THE COURT: Yes.

REDIRECT EXAMINATION

BY MR. KENNEDY:

Q **So, Dr. Budoff, I'm going to jump around a few topics you covered with Mr. Klein just now.**

Mr. Klein asked you about whether Vascepa was suitable to reduce triglycerides in severely hypertriglyceridemic patients in less than 12 weeks.

Do you remember that discussion?

A **Yes.**

Q **And you do you remember the related discussion with Mr. Klein about whether triglyceride levels are reduced in less than 12 weeks? Do you remember that testimony?**

A **Yes.**

Q **Now, once a severely hypertriglyceridemic patient's triglyceride levels have been reduced, is therapy complete?**

A **No.**

Q **Why not?**

A **Well, again, if you stop the therapy, in most cases it will go back up. We've seen that in the MARINE trial. We see that in clinical practice, that in a vast majority of patients triglycerides will not say below 500 without additional medical therapy.**

Q **What is the therapeutic goal for a patient with severe hypertriglyceridemia?**

A **The goals and the guidelines are to reduce and maintain their triglycerides below 500 milligrams per deciliter.**

Q **Now, for a severely hypertriglyceridemic patient who doesn't have what we've been calling one of the reversible causes of severe hypertriglyceridemia, how do you maintain a reduction in triglyceride levels?**

A **So in almost all cases I continue the therapy long-term, as I've described this morning and this afternoon.**

Q **With your typical patients who have very high triglycerides or severe hypertriglyceridemia, would you know if they had reduced their triglycerides below 500 in fewer than 12 weeks?**

A **No. I don't usually bring them in for lab testing at a shorter interval.**

Q **Do you know of any clinicians who do, as a habit?**

A **No. I think the vast majority, if not all physicians that I'm aware of, their practice patterns revolve around what we would call a typical practice, and a typical practice would**

be to repeat the results at three months, to bring them back at three months for a follow-up visit.

Q Now, Mr. Klein also asked you on cross about whether your patients ever take Vascepa for less than 12 weeks.

Do you remember that testimony?

A Yes.

Q And I think you said that some of your patients do take Vascepa for less than 12 weeks. Do you remember that?

A Yes.

Q Now, have you ever prescribed Vascepa to a patient with severe hypertriglyceridemia for fewer than 12 weeks?

A No. The shortest prescription I've ever written would be a one month prescription with three refills. So that would be four months, at a minimum, to get them to the three-month follow-up, where I can reassess their lipids.

Q So I think you alluded to some reasons why one of your patients might, nonetheless, take Vascepa for fewer than 12 weeks. Can you explain what those reasons are.

A Yeah. So most commonly they go to the pharmacy, and the price is too high, and they say, "I can't afford it," and so they don't want to take it, and they call me and they say, "Can I take something else?"

Second most commonly would be side effects. Patients perceive side effects, even though Vascepa I consider generally safe. I would say that Vascepa is -- has some side

effects and some issues with tolerability. So some people would say, "Oh, I feel joint aches," or, "I'm getting some other problem. I'm going to stop the therapy before 12 weeks."

Q Now, you had a discussion with Mr. Klein about whether there are patients with very high triglycerides who can have their condition addressed solely with diet and lifestyle.

Do you remember that discussion?

A Yes.

MR. M. KENNEDY: Mr. Brooks, can we have PX 989. This is ATP III guidelines we a looked at earlier today.

COMPUTER TECHNICIAN: Madam clerk, can you switch me?

MR. M. KENNEDY: And, Mr. Brooks, if you'd go to page 195 of the document and blowup the left-hand column.

BY MR. M. KENNEDY:

Q So, Dr. Budoff, do you recognize this passage?

A Yes.

Q I think we discussed portions of this earlier today.

A Yes.

Q I would like to direct you a few lines down, and the heading of this passage is Very High Triglycerides. What is your understanding of why this passage is headed that way?

A This is the part of the document that addresses severe hypertriglyceridemia.

MR. M. KENNEDY: So, Mr. Brooks, I would like to go about ten lines down and highlight the sentences beginning with "weight reduction and increased physical activity," and go through the word "pancreatitis," about five lines down.

BY MR. M. KENNEDY:

Q **And, Dr. Budoff, if you could review this passage and let me know what, if anything, does this passage tell you about the clinical needs of patients with severe hypertriglyceridemia?**

A **Well, it's just saying that after lifestyle modifications are emphasized, triglyceride-lowering drugs are usually required. So, it just tells you that most patients -- as we discussed this afternoon, most patients fail diet and exercise as a primary treatment strategy.**

Q **And what if a patient succeeds with diet and lifestyle changes?**

A **Well, if they were successful, then they would not be indicated to start Vascepa, and I would just continue lifestyle changes, as least for the MARINE indication purposes of discussion.**

Q **So you also had some discussion with Mr. Klein about LDL-C. Do you remember that testimony?**

A **Yes.**

Q **What would a clinician in your field know about LDL-C, just whether it's good or bad, what its function is?**

A **I would hope that every person who is practicing in the field of lipids understands that LDL cholesterol is bad.**

Q **And they would understand that, all things being equal, it would be better to have low LDL-C rather than high LDL-C?**

A **Yes.**

Q **Is this knowledge that clinicians in your field would have in their minds when reviewing the Vascepa labeling and particularly the clinical data?**

A **Yes.**

Q **Is this background knowledge -- would that affect your treatment decisions for patients with severe hypertriglyceridemia?**

A **That would really be the only reason, short of the REDUCE-IT indication, to use Vascepa preferentially over the less expensive fibrates or Lovaza which has a generic alternative.**

So, we go through great steps to get patients on Vascepa right now. I have to often call the insurance company. I have to convince them that my patient meets the criteria. I have to then sometimes get a formal prior authorization approved.

So I go through steps. The patient has to pay extra money at the pharmacy, all of that. The primary reason is not because it's the best triglyceride-lowering drug, but because it's the best drug at not -- that lowering triglycerides will

not affect that LDL cholesterol.

So, I think that becomes paramount in the clinician's decision to use Vascepa over generic alternatives.

Q So just to be clear, these considerations that you just mentioned, do they affect your decision about which medication to prescribe with patients with severe hypertriglyceridemia?

A Absolutely.

Q So Mr. Klein asked you some questions about the clinical effects experienced by patients who take Vascepa, and particularly whether some patients may not achieve the clinical effects touted in the clinical trial section of the label. Do you remember that testimony?

A Yes.

Q Now, when you administer Vascepa to a patient by writing a prescription, and a patient with severe hypertriglyceridemia, what clinical effects do you expect to achieve at the moment you write that prescription?

A So my intent is that they will follow the general results of the MARINE trial, that they will get a triglyceride reduction of about a third, that their LDL cholesterol will not go up, that their apo B will go down.

Obviously there are patient-to-patient differences. That's why I have to retest them at 12 weeks to see what really happened in my patient.

Q So what percentage of your patients end up achieving the

effects touted in Table 2 of the labeling, that is, severely hypertriglyceridemic patients to whom you prescribe Vascepa according to the labeling?

A Yeah. So we know it's about three-quarters of patients will achieve that general result, and there will be some people on the outsides of that, the extremes.

Q I think you called them outliers in your discussion with Mr. Klein?

A Yes.

Q So at the moment you write the prescription to a patent with very high triglycerides, do you have any way of knowing whether that patient is going to be an outlier?

A No.

Q So, I would like to ask you couple questions about apo B.

So am I -- is treating very high triglycerides with Vascepa in order to reduce triglycerides and lower apo B, is that on-label?

A Yes.

Q Is that part of your prescribing practice to patients with very high triglycerides?

A Yes.

Q And, finally, I would like to go to a document that Mr. Klein used with you, it's your reply expert report, and this is PX 177.

MR. M. KENNEDY: And, Mr. Brooks, if you could

turn to page 23 of this document.
BY MR. M. KENNEDY:
Q Now, Mr. Klein showed you paragraph 54 of your expert report, and 57, but I would like to show you a couple surrounding paragraphs that he didn't show you, and starting with paragraph 53.
MR. M. KENNEDY: And, Mr. Brooks, can you blow that up, please. And maybe put 53 along with 54, if you're able to do that.
BY MR. M. KENNEDY:
Q Now, Dr. Budoff, again, Mr. Klein showed you 54. He didn't show you 53. Could you just review 53 and then tell us what was the context in which you were giving the opinions that Mr. Klein showed you in 54?
A (Witness reviews document.)
Yeah. So this is suggesting that even though Dr. Sheinberg has given them the medication, that he's instructed them to wait six weeks before filling the prescription and then coming back at 12 weeks. Therefore, when they return, they've only received six weeks of therapy and not 12 weeks of therapy.
Q Do you agree with Dr. Sheinberg's theory as stated in paragraph 53?
A This has, to my knowledge, never been practiced this way, and this would not be how any physician that I've ever

encountered would prescribe medication.

We give them the prescription and say start this medicine. And if we don't want them to start the medicine, we wouldn't give them the prescription.

I don't give them a prescription and say put in your calendar for six weeks from now to go to the pharmacy and fill this. That would not work in clinical practice, and it's not recommended approach to treatment.

Q Now, at the time you wrote this reply expert report, you gave a number of reasons why you disagree with Dr. Sheinberg; is that right?

A Yes.

Q And Mr. Klein did show you a couple of those reasons in paragraphs 54 and 57; is that right?

A Yes.

Q Now, he didn't show you paragraph 55, which Mr. Brooks has kindly put on the screen. And I'll read it into the record.

"To begin with, the Prescribing Information counsels that the drug should be given to patients for whom efforts to reduce their triglycerides below 500 milligrams per deciliter, using only diet and lifestyle modifications, have been unsuccessful."

Do you see that?

A Yes.

Q **Now, you reference the Prescribing Information. Are there particular portions of the Prescribing Information that counsel that drug should only be given to patients who can't reduce their triglycerides below 500 without -- through just diet and lifestyle?**

A **Yes.**

Q **Which portions do you have in mind?**

A **Well, we talked about Section 2, the dosing and administration. I think that explicitly states that you should use diet and lifestyle. The patient should engage in diet and lifestyle before using therapy, and then, obviously, if they're still not at goal, you would put them on therapy.**

Also, the Section 14, the clinical trial section, we know and we reviewed that this afternoon as well, the MARINE trial was done with that six- to nine-week washout period where they documented that after diet and lifestyle failed, if their triglycerides were still above 500, were then they enrolled in the study.

Q **Now, people who are able to reduce their triglycerides below 500 with diet and lifestyle, is Vascepa indicated for those patients?**

A **Well, now it is. The REDUCE-IT indication may play a role depending on their underlying cardiovascular risk. But for severe hypertriglyceridemia, the MARINE indication, it would not be indicated.**

MR. M. KENNEDY: Your Honor, I have no further questions.

THE COURT: Mr. Klein?

MR KLEIN: No further questions.

THE COURT: All right. Thank you, Dr. Budoff. You may step down.

THE WITNESS: Thank you very much.

MR. SIPES: Your Honor, Christopher Sipes for Amarin. With that, plaintiffs close their opening case.

MR KLEIN: Your Honor, Ms. Fundakowski is going to address the fact that plaintiffs have closed their case, and Ms. Fundakowski will make a motion.

MS. FUNDAKOWSKI: Claire Fundakowski on behalf of the defendants Hikma.

Your Honor, we understand that this is a bench trial, but if Your Honor is so inclined, defendants would like to move for a judgment on partial findings under Rule 52(c).

Plaintiff's sole infringement theory is that defendants --

THE COURT: Now, you need -- I don't know if you're reading from something. You need to slow down if you are reading because, otherwise, the court reporter will remind you to slow down. I also want to take some notes, so you need to indulge me.

MS. FUNDAKOWSKI: Thank you, Your Honor.

Plaintiff's sole infringement theory is that defendants' proposed labels will actively induce doctors to infringe the claims. To prevail, plaintiff's must show by preponderance of the evidence that defendants have the specific intent, based on the contents of their proposed labels, to encourage physicians to prescribe defendants' ANDA products in an infringing manner. Plaintiffs have failed to meet this burden.

Among other limitations, each of the asserted claims requires at least 12 weeks of treatment. As recognized in the Court's summary judgment order and confirmed by today's testimony, defendants' proposed labels do not explicitly tell doctors they should prescribe the drug for at least 12 weeks.

Plaintiffs therefore argue that the Court should infer that defendants induce infringement because defendants' proposed labels instruct doctors to treat severe hypertriglyceridemia as an adjunct to diet.

Plaintiffs' evidence fails to show that defendants' proposed labels induce physicians to prescribe icosapent for at least 12 weeks.

Under *Grunenthal*, 919 F.3d 1333 at 1339, even if the indicated use includes the patented use, there is no inducement if the proposed labels do not specifically encourage the patented use.

The rationale for the Federal Circuit's

Grunenthal **decision is rooted in plaintiff's burden to prove that defendants possessed specific intent to induce infringement.**

Because the plaintiff in that case could not show that the indicated use was coextensive with or required the patented use, the Court could not infer that defendants had a specific intent to induce infringement.

The Federal Circuit reached this conclusion in ***Grunenthal*** **even though plaintiff presented evidence that, I quote, "most of the uses of their proposed ANDA products would be directed to," end quote, the claimed use. And that was at 1340.**

Here, for the same reason, plaintiffs have failed to show that defendants' proposed labels will induce prescribers to treat patients for at least 12 weeks. The undisputed evidence that defendant proposed -- show that the defendants' proposed labels are indicated for conditions that do not require treatment --

THE COURT: Where is the undisputed evidence?

MS. FUNDAKOWSI: I believe we heard Dr. Budoff testify today that severe hypertriglyceridemia has, I quote, reversible causes, which according to Dr. Budoff would, I quote, not be considered a chronic condition.

Dr. Budoff agreed with plaintiffs' invalidity expert, Dr. Toth, that severe hypertriglyceridemia, I quote,

can be acute -- an acute phenomenon.

Dr. Budoff testified that weight loss of 5 percent to 10 percent can result in a 20 percent decrease in triglycerides. He testified that it is possible to see reductions in triglycerides of up to 50 percent without any medication.

And even in the MARINE study, in the patient population that received four to six weeks of diet and exercise, they were unable to reduce their triglycerides. Dr. Budoff testified, and as shown in DX 1701-51, that about 21 percent of patients falling within the scope of defendants' proposed indication can reduce and maintain their triglycerides down to below 500 milligrams per deciliter with diet and exercise alone, or, in other words, without the need for continued drug treatment for at least 12 weeks.

Plaintiffs' evidence therefore fails to show that the Court can infer that defendants' proposed labels induce doctors to prescribe icosapent for a period of at least 12 weeks.

Plaintiffs argue that specific intent to induce infringement can be inferred because, according to plaintiffs, defendants' proposed labels would inevitably lead some physicians to prescribe icosapent for at least 12 weeks, but plaintiff's misstate the legal standard.

The Federal Circuit has never held that

inducement can be inferred if only some physicians will eventually infringe. Rather, the law merely holds that an instruction to infringe need not be directed to all physicians in order for there to be inducement.

This case law does not apply here because there is no such instruction inducing infringement. For example, in *Eli Lilly*, 845 F.3d 1357 at 1369, the Court found that repeated instructions and warnings throughout defendants' proposed labeling demonstrated specific intent to induce infringement.

As explained at 1368, the Court explained that the instructions teach an infringing use such that we are willing to infer from those instructions an infirmative intent to infringe the patent.

The Federal Circuit there did not require evidence that all physicians would follow those repeated instructions and warnings, but in light of the unambiguous, repeated instructions and warnings, the Court explained at 1369 that it was sufficient that those instructions, I quote, would inevitably lead some physicians to infringe.

Likewise in *Vanda*, 887 F.3d 1117 at 1131, the court found that there was a recommendation to perform the claimed genotyping test. The label did not require all physicians to perform the genotyping test, so it was again sufficient that defendants' labels would inevitably lead some

physicians to infringe.

Here defendants' proposed labels do not contain an explicit instruction that defendants' products should be administered for at least 12 weeks. As in *Grunenthal*, defendants' proposed labels likewise do not implicitly require a 12-week treatment.

Plaintiffs have thus failed to meet their burden to show induced infringement, and defendants respectfully request judgment in their favor.

THE COURT: Thank you.

MS. FUNDAKOWSI: Thank you, Your Honor.

THE COURT: Mr. Sipes, will you be responding?

MR. SIPES: If the Court would like, I can respond, Your Honor.

THE COURT: Well, I would like some response.

MR. SIPES: That was my question. I wasn't asking to choose. I wanted to make sure the Court did not just want to just take it under submission.

THE COURT: I'm going to give you a ruling, so I want a response.

MR. SIPES: Okay.

I understand them to be moving principally on the 12-week limitation, so I will respond on that.

The issue here is one of whether or not the labeling induces administration of the drug for at least

12 weeks. First, let me go through the evidence that shows that it does, and then I will address the legal standard question.

Dr. Steve Ketchum testified about FDA's review and negotiation over the labeling, and pointed to a number of documents both public that would help explain to physicians what the scope of the approval was, and otherwise that showed that the indication for which the drug was approved, treatment of severe hypertriglyceridemia, is chronic, and that treatment is to reduce and maintain triglyceride levels below 500 which requires treatment more than 12 weeks.

And, in fact, then Dr. Budoff went on and explained how physicians understand the labeling, and that the labeling is understood to require clinicians to maintain triglyceride levels in these patients under 500, and that as a chronic condition that requires indefinite treatment. He went through all the other elements of the claims as well and showed that they were met too.

There's no question that the labeling is instructing physicians that the drug may be used to treat the chronic condition of severe hypertriglyceridemia, to maintain triglycerides below 500, and that that will go on for 12 or more weeks.

In fact, Dr. Budoff went on and said that the dosage and administration section instructs doctors rule out

the reversible causes. So it in fact specifically directs physicians towards chronic patients, towards 12 or more weeks treatment.

In terms of the case law, for example, in *Astrazeneca v. Apotex*, 633 F.3d 1042, Federal Circuit 2010, the Federal Circuit addressed a case in which the (inaudible) had actually carved out an indication for once daily administration that the claim was directed to, their labeling instructed for twice daily administration, but also included titration language, that physicians should seek to use the lowest possible dose, and Federal Circuit found there that that would inevitably lead some physicians to treat once a day, that that was sufficient for induced infringement.

That case was actually endorsed by the *Vanda v. West-Ward* case, 887 F.3d 1117, Federal Circuit 2018, which rejected the line of argument, I believe, that the defendants are making now, that we need to show that all physicians would be led.

In this case, we have clear instructions in the labeling to rule out reversible causes. We have clear instructions to treat patients for a chronic condition. We have descriptions of the clinical study section, which shows as well that the drug is safe and effective for 12 or more weeks. There was no instructions to treat any shorter period of time.

And, we have accompanying FDA review documents available to the public that would further inform physicians as to the meaning of the labeling the defendants are proposing, and we think that more than meets the standard for induced infringement in this case.

Thank you, Your Honor.

THE COURT: Thank you.

MR. SIPES: If there are no questions.

THE COURT: Any rebuttal?

MS. FUNDAKOWSI: If I may, Your Honor.

Your Honor, I would like to make two points. Claire Fundakowski again.

We believe *Grunenthal*, 919 F.3d 1333 at 1340, is completely on point here. Mr. Sipes mentioned a case, I believe it was the *Astrazeneca v. Apotex* case, in which the dosage and administration section included express instructions for patients to titrate down the medication.

***Grunenthal* distinguished that case explaining -- and, again, this is at 1340 -- that *Astrazeneca* is in apposite to our facts. There was specific intent that could be inferred, I quote, because the defendant proceeded with a plan to distribute the generic drug knowing that its label imposed infringement problems.**

In addition, the instructions in the Dosage and Administration Section of the label would inevitably lead some

consumers to practice the claimed method of once daily dosing by encouraging users to taper downward to the lower -- lowest effective dose.

The language in that Court's decision that "some users" would be led to infringe is because not all physicians would be required to use the lowest effective dose. Not all physicians would be required to taper down to that dose. But there was an express instruction in that case, and that -- such an instruction is absent here.

I would also like to point out Mr. Sipes referenced the FDA forms that mention chronic use. But as noted -- just a moment, please -- as noted in *Horizon*, 940 F.3d 680 at 702, knowing of the possibility of infringement will not suffice.

Of course, Vascepa can be used long-term. It can also be used short-term. The label is indifferent to the length of treatment and leaves it entirely up to physician discretion. This does not show active intent to induce infringement and therefore defendants believe judgment should be granted in their favor.

That's all, Your Honor.

THE COURT: Thank you.

I want to take some time to formulate my ruling. I want to continue with the defendants' rebuttal portion.

Are you ready to proceed?

MR. REIG-PLESSIS: Yes, Your Honor.

Your Honor, my name is Eimeric Reig, I'm counsel for the defendants here, and as defendants' first witness, we call Dr. Jonathan Sheinberg.

THE COURT: Thank you.

THE CLERK: Would counsel like to please have someone come up and retrieve these exhibit binders?

MR. REIG-PLESSIS: And we would also ask permission to approach. We have some witness binders, as well, for Dr. Sheinberg.

THE COURT: Yes.

JONATHAN I. SHEINBERG, M.D.,
called as a witness on behalf of the Defendants,
was sworn and testified as follows:

THE CLERK: Please be seated.

Please state for the record your full name and spell your last name.

THE WITNESS: Jonathan Sheinberg, S-h-e-i-n-b-e-r-g. Jonathan, J-o-n-a-t-h-a-n.

MR. REIG-PLESSIS: Good afternoon, Dr. Sheinberg.

THE WITNESS: Good afternoon.

DIRECT EXAMINATION

BY MR. REIG-PLESSIS:

Q Where are you currently employed?

A I'm currently employed in Austin, Texas, for Baylor Scott

& White Cardiology.

Q And what is your current position at Baylor Scott & White Cardiology?

A I am a senior staff cardiologist. I am an invasive cardiologist with an interest in preventive cardiology as well.

Q Did the defendants retain you to testify as an expert in this case?

A Yes, they have.

Q Now, apart from this case, do you have any affiliation with the defendants?

A I do not.

Q And you mentioned that you are a general cardiologist with an interest in preventive cardiology. Could you just explain what preventive cardiology is.

A Yes, sir. So I have general cardiology experience, in other words, I practice the full gamut of cardiology from initial evaluation of a patient with intent to prevent that patient from developing coronary disease, taking a patient who already has developed coronary disease and preventing that patient from having a secondary event.

I also treat general cardiology patients.

I'm also proficient in the catheterization laboratory in which we perform invasive procedures to evaluate problems.

THE COURT: Also, would you make sure you speak into the microphone. I want to make sure everyone is able to hear you. Thank you.

THE WITNESS: Yes, ma'am.

BY MR. REIG-PLESSIS:

Q So turning first to DDX 4.1, there is a snapshot on the screen of DX 2225, page 1, which is in your binder as well.

Could you identify this document, please.

A Yes, this is my CV.

Q Does your CV accurately summarize your educational background, work experience, and research?

A Yes, it does.

MR. REIG-PLESSIS: And, Your Honor, we would move into evidence DX 2225.

MS. KEANE: No objection, Your Honor.

THE COURT: 2225 is admitted.

(Defendants' Exhibit 2225 received in evidence.)

BY MR. REIG-PLESSIS:

Q So turning to DDX 4.2, there's another snapshot on the screen of the same exhibit DX 2225.

Could you summarize your educational background for the Court, please.

A Yes, I can. I graduated with a bachelor's degree from Washington and Lee University. I attended Georgetown University School of Medicine where I received my medical

degree.

At that time I entered active duty with the United States Air Force and did my internship at Georgetown and Fairfax Hospital and my residency at Keesler Air Force Base in internal medicine, that's in Biloxi, Mississippi.

After completion of my internal medicine residency, I went to Wilford Hall Air Force Base -- I'm sorry -- Wilford Hall Medical Center at Lackland Air Force Base, Texas, to finish my fellowship in cardiovascular disease.

After completing that, I continued to serve in the Air Force for an additional four years with a combat deployment overseas before settling in Austin, Texas, in 2004, which is where I am living now.

Q Do you have any board certifications currently?

A I'm Board Certified in cardiovascular disease.

Q And how long have you been a cardiologist?

A This is my 20th year.

Q How many patients do you see per month, approximately, in your cardiology practice?

A I see roughly a 100 patients or more per month -- I'm sorry, per week, which averages about 400 or so, plus or minus, per month.

Q Do you treat patients with elevated triglycerides?

A Every day.

Q Do you treat patients with triglyceride levels above 500?

A **Yes, I do.**
Q **How often?**
A **Relatively frequently, on the order of approximately 20 to 30 per month.**
Q **Have you prescribed Vascepa before?**
A **Yes, I have.**
Q **And have you taught courses relating to cardiology?**
A **Yes, I have. I have been an instructor and a professor of medicine both at the University Uniform Health Science Center in Bethesda, Maryland, as well as Wright State University in Dayton, Ohio.**
COURT REPORTER: Slow down, please.
THE WITNESS: Sorry. So the Uniform Services University in Bethesda, Maryland, as a Clinical Professor, as well as an Assistant Professor at Wright State University in Dayton, Ohio. I'm currently an Assistant Professor of Medicine at the University of Texas Medical Branch in Galveston.
BY MR. REIG-PLESSIS:
Q **And do you conduct any other activities related to cardiology?**
A **Yes, I do. As the first page of my CV pointed out, not only am I a cardiologist, but I'm also one of the few physicians in the United States who is a sworn police officer.**
I serve in that capacity, not only as an officer,

but I work within the Department of Justice to develop and create wellness programs which we institute throughout the United States and Canada to keep police officers and other first responders healthy as well.

Q Now, do you have any publications on your CV?

A I do not.

Q And why not?

A I am a practicing, busy, what we like to refer to as, quote, in the trenches, cardiologist. With a very busy clinical practice, there's really no time left to devote to research.

In fact, we often in -- those of us who practice in busy, clinical practices often say that we are penalized if we spend time doing research because at that time we are not actively seeing patients and we are not generating volume through the clinic.

So I do not have any research publications in that regard.

Q Now, we've heard some testimony already today about approved drug labels. Are those labels generally directed to researchers or to clinicians?

A They're directed towards clinicians.

Q And are you a clinician?

A Yes, sir, I am.

MR. REIG-PLESSIS: Defendants now tender

Dr. Sheinberg as an expert in the field of cardiology.

MS. KEANE: No objection, Your Honor.

MR. REIG-PLESSIS:

Q Dr. Sheinberg, do you have slides --

THE COURT: Is this just a general field of cardiology?

MR. REIG-PLESSIS: Yes, Your Honor.

THE COURT: Is that the motion?

You have to wait for me to rule. So, is that the motion?

MR. REIG-PLESSIS: Yes, Your Honor, in the general field of cardiology.

THE COURT: There's no objection, so the request is granted.

BY MR. REIG-PLESSIS:

Q Dr. Sheinberg, do you have slides to assist the Court with your testimony today?

A Yes, I do.

Q And are the documents cited in those slides documents you relied on in forming your opinions?

A Yes, they are.

Q So turning now to DDX 4.3, could you summarize the opinions you'll be presenting in your testimony today.

A Yes, I will.

I will -- it will be my opinion this afternoon that

severe hypertriglyceridemia is not necessarily a chronic condition which requires indefinite drug treatment, and I also will opine that severe hypertriglyceridemia can be treated with a short course of drug therapy followed by diet and exercise to maintain the triglyceride reductions that we have seen.

Q And, Doctor, are you offering those opinions today in the context of the indicated use for Vascepa and defendants' products to treat, quote, severe hypertriglyceridemia?

A Yes, I am.

Q So turning to DDX 4.4, do you also have specific opinions on defendants' product labels?

A Yes, I do. It is the opinion that I will share today that defendants' labels do not encourage, recommend, promote, or require administration -- administering their product for any duration, let alone at least 12 weeks, to achieve specific effect on the lipids, including a minimum percent reduction in triglycerides, to avoid an increase in LDL, and to cause a reduction of apolipoprotein B levels.

I will also show this can be done without concurrent lipid-altering therapy.

Q Turning to DDX 4.5, in forming your opinions did you analyze the claims that are asserted by Amarin in this case against the defendants?

A Yes, I have. '929 patent claims 1 and 5; '728 patent

claims 1 and 16; '715 patent claim 14; '677 patent claims 1 and 8; '652 patent claim 1; and '560 patent claims 4 and 17.

Q And are you familiar with those claims which are in the patents that are in your binder?

A Yes, I am.

Q Turning to DDX 4.6, which limitations of the asserted claims did you specifically analyze?

A In regarding the at least 12 weeks duration of drug treatment limitation, that is in all 10 asserted claims.

In regards to the specific effects on lipid levels limitation, which includes the minimum triglyceride reductions;

The no increase in LDL; and

The reduction in apolipoprotein B that is seen in nine claims which are all asserted claims except '929 patent claim 1; and

The limitation of no concurrent lipid-altering therapy, which we will discuss, which includes statins, but not limited to that drug class is in three claims;

'728 patent claims 1 and 16; as well as '715 patent claim 14.

Q And are you addressing any other limitations of the claims in your testimony besides the limitations described in DDX 4.6?

A No, sir, I am not.

Q So turning to DDX 4.7, there is a snapshot from DX 1500, which I understand is on the admitted exhibits list, could you point out the three categories of limitations that you analyzed in an exemplary asserted claim.

A Yes. In this example, which is '728 patent claim, you can see that it does have all three of the limitations. Starting with the yellow highlighted section number 1 for a 12-week duration, as you can see it describes that acid or esters for a period of 12 weeks.

In regards to the specific lipid effects, the example here which is seen in nine claims, to effect a reduction in triglycerides without substantially increasing LDL.

And the third example, which is highlighted in orange, is seen under the section after 1500 milligrams per deciliter, talking about individuals who do not receive concurrent lipid-altering therapy as this is one of the claims that has all three components associated with it.

Q So turning now to DDX 4.8, there are snapshots on the screen of the Court's claim construction order, and the parties' stipulation on agreed upon constructions which are ECF numbers 135 and 83. Did you apply the constructions in these documents in forming your opinions in this case?

A Yes, I have.

Q So turning to DDX 4.9, what are the topics you intend to

address in your testimony?
A There will be two specific topics. The first I will give background regarding the concept of severe hypertriglyceridemia, and we will -- I will also talk about how Vascepa is used, and then we will discuss the noninfringing analysis that I performed.
Q So turning to DDX 4.10, there is a snapshot on the screen of DX 1876, page 99. We understand this exhibit has also been admitted. Could you identify this document.
A Yes, I can. This is the National Cholesterol Education Program, the NCEP expert panel on detection, evaluation, and treatment of high blood cholesterol levels in adults, otherwise known as the Adult Treatment Panel, or ATP III final report. It was published in circulation in 2002.
And, as this document goes on to describe in the highlighted area below, it states that if triglycerides are very high, which is greater than or equal to 500 milligrams per deciliter, attention turns first to the prevention of acute pancreatitis.
Q And what is severe hypertriglyceridemia or very high triglycerides?
A In terms of the definition here, greater than 500 milligrams per deciliter, is that the --
Q Yes. Just in general what is it?
A It's a situation in which hyper means too many.

Triglyceridemia means triglycerides in the blood, and so it's too many triglycerides in the blood.

Q **Now, is severe hypertriglyceridemia a discrete disease?**

A **It is not actually a discrete disease. It is more of a downstream consequence of multiple potential etiologies or causes.**

Q **Why does severe hypertriglyceridemia require treatment?**

A **Because if it is not treated, we know it can cause two different issues, the first which is described here as pancreatitis. Pancreatitis, which has already been described as a very painful, horrible condition in which the pancreas becomes inflamed and essentially begins to digest itself.**

Not only is it painful, but it carries with it a rather high mortality rate. In other words, it can cause death in a relatively frequent amount of people who suffer from it.

And we also know that there is an association with elevated triglycerides in cardiovascular risk.

Q **Now, if a patient is at risk for pancreatitis, do you delay treating that patient with triglyceride-lowering drugs?**

A **Absolutely not. If I have a patient that is at risk for this potential life-threatening complication, we treat that person aggressively from day one.**

Q **Do you necessarily treat patients differently depending on whether their triglycerides are above or below 500?**

A **There is no magic thing that happens at 500. If I have someone who has triglycerides of 400, someone who has triglycerides of 550 or 600, I will look at that person relatively equivalently and treat those people aggressively to prevent the sequelae or the consequences that those triglycerides would potentially result in.**

Q **So turning to DDX 4.11, there is a snapshot on the screen of DX 1982, page 2 which is already in evidence. Could you identify this document.**

A **Yes, I can.**

This is the website for Vascepa, and the website goes on to describe what are the causes for hypertriglyceridemia, and it lists five specific issues. The first two are highlighted in yellow here.

Oftentimes, as the testimony has shown throughout the day, these two things run hand-in-hand, but according to the website here it quotes, "Here are some ways that triglyceride levels may become very high."

The first is diet and lack of exercise. This combination of poor diet and a sedentary lifestyle is the cause of most of what we see. I would imagine that's why they are the two items that are listed first. And after practicing for 20 years with 25,000 patients in my population that I see, it is no question in my mind that these are the primary causes of hypertriglyceridemia.

Under the diet section, it says what you eat and drink, especially alcohol and processed carbohydrates. Quite frankly, the concept, at least where I practice in Texas, sugared sodas should be listed on that list because it is a considerable problem that we see. We also know that our patients are likely not getting the exercise that they need.

Besides diet and exercise, we see certain medical conditions which can cause hypertriglyceridemia such as diabetes.

And I would go on to also say, in regards to diabetes, most of the diabetes that we treat in cardiology is Type II diabetes, it's diabetes that results from what we call insulin resistance which is a diabetes not from a genetic, discrete problem in which the pancreas doesn't produce enough insulin, it's from a metabolic problem which is basically a diet and exercise issue.

The fourth thing on the list are specific drugs, which includes hormones and certain blood pressure medications.

And the last thing on this list, it says genetics, and that's a rather broad term, which if I may define it a little bit at this moment.

There are two -- we can think of the genetic issue as basically two different discrete issues. There is a definitive, genetic abnormality in a very small minority of

our patients that are missing the genetic ability, or missing the ability to code for certain enzymes or proteins, which, for example, cause triglycerides to be broken out of certain cholesterol particles.

For example, there's an enzyme called lipoprotein lipase, and if there is an individual who does not have that enzyme, that individual will have severely elevated triglycerides which are what we call refractory or very difficult to treat.

There are other genetic abnormalities. They've already been mentioned here this morning and this afternoon. But, 98 or more of our patients -- 98 percent or more of our patients do not have those discrete genetic abnormalities.

What they may have is what we like to call a genetic predisposition. In medicine we understand that there are genetic predispositions for everything, for how tall people are, for how people respond to certain diets and exercise.

We all know people who -- the layman's term is they look at a pizza and they gain weight. We know people who are able to eat very little and still not achieve optimal body mass, and the other side of the spectrum is true as well. We know people who can eat everything on their plate and they never gain weight.

We have genetic proclivities that influence how we respond to everything in our lives, and there are people who

have a genetic proclivity to have elevated triglycerides without having the specific genetic abnormality which relates in exceedingly elevated triglyceride levels.

Q So can a patient be genetically predisposed to hypertriglyceridemia that is not severe?

A Absolutely.

Q Now, apart from those listed on Amarin's website, are there other cases of severe hypertriglyceridemia?

A There are. Under medical conditions we have -- we see renal failure. We see people who smoke have an increased risk. We know in pregnancy, especially in the last trimester, women can have hypertriglyceridemia which sometimes becomes severe.

So there are certainly other things that this list is exclusive of.

Q Are there short-term causes of severe hypertriglyceridemia?

A Absolutely. We know it for a fact that when people overindulge in certain diets, a diet which is very high in simple sugars or alcohol, and potentially reduce their activity -- the best example of this I can think of is you take someone who goes on a cruise, who is potentially genetically predisposed to have elevated triglycerides. They're on the cruise for the week. They are eating at the buffet, having as many desserts as they want, they're not

exercising. They're consuming considerable amounts of alcohol.

That individual, who is genetically predisposed for an elevation of triglycerides, even severe elevation of triglycerides, after that cruise there's a very good chance that individual will be over 500.

So there are acute conditions. You remove those acute insults, you take the person off the cruise, they go back on their lifestyle, and that situation of hypertriglyceridemia can potentially resolve. So there are certainly other acute reasons.

Q Now, does Amarin's website indicate anywhere that the use of Vascepa is limited to patients with genetic abnormalities causing severe hypertriglyceridemia?

A No, sir, it does not.

Q And what are the typical triglyceride levels of patients with those types of genetic abnormalities?

A The genetic abnormalities that I mentioned, the ones that have already been mentioned earlier in testimony, are typically well over 1000 to 2000.

Again, there's a considerable variability, but those people who have discrete genetic conditions typically have triglycerides which are multiples of 500.

Q So generally, in the triglyceride range of 500 to 1000, does that include patients with genetic abnormalities usually?

A It can, but usually it does not. As we get higher, up to that 1000 level range, the genetic abnormality will become more prevalent.

But when we talk between 500, as we get higher in that range, there are still plenty of people who will have severe hypertriglyceridemia which is not from a discrete genetic abnormality.

Q And when you say "plenty of people," can you estimate what percent of patients would have it?

A Ninety-seven plus percent, 98 percent.

Q And just to be clear, that's 98 percent without a genetic abnormality?

A The discrete -- excuse me. The discrete genetic abnormalities really occur in potentially 2 percent of the population that we see.

Q So turning now to DDX 4.12, there's a snapshot on the screen of DX 1953, page 29. Could you identify this document.

A Yes, I can. This is Amarin's validity contentions.

This document goes on to say that -- in the first paragraph here,

> "Persons of ordinary skill in the art also understood that both diet and exercise level could have significant impacts on triglyceride levels. Heavy consumption of carbohydrates, certain kinds of fats and/or alcohol was understood to lead to

increased triglyceride levels."

The document further goes on to say in the second paragraph,

"In contrast, it was understood that regular exercise could offset the triglyceride effects of some dietary factors and decreased triglyceride levels. Accordingly, the lack of exercise and/or sedentary lifestyle are known to correlate with higher triglyceride levels."

Q Do you agree with these statements in Amarin's validity contentions in this case?

A Absolutely. This is what I would consider the absolute, primary reason many of our patients suffer from hypertriglyceridemia.

MR. REIG-PLESSIS: And, Your Honor, we would move the admission of DX 1953.

MS. KEANE: Your Honor, plaintiffs object to the admission --

THE COURT: Would you make sure you speak into the microphone.

MS. KEANE: Yes, Your Honor.

Plaintiff's object to the admission of DX 1953. These are Amarin's preliminary validity contentions. It is a document containing attorney argument. It is not evidence of fact, and it, therefore, is not appropriate admissible

evidence.

We are aware of there is case law --

THE COURT: Isn't it already part of the record?

MS. KEANE: They have not been admitted, Your Honor.

THE COURT: Well, wasn't it a record in terms of it being filed with the Court on the docket?

MS. KEANE: No, Your Honor. It was not filed, it was just exchanged amongst the parties. It's a preliminary statement --

THE COURT: Oh, I see.

MS. KEANE: -- of positions of counsel.

THE COURT: I'm sorry to interrupt. But, you were saying --

MS. KEANE: Yes. We believe there's a case from the District of Hawaii that's directly on point, that preliminary contentions, one, are not evidence of fact, and, two, they are not party admission either. And the cite for that is 2015 WL 1117993, and the title is *Kowalski v. Anova Food*.

THE COURT: What's your response?

MR. REIG-PLESSIS: Well, Your Honor, a couple responses. I think we're a little puzzled by the objections since these are Amarin's own statements and contentions in this very case. We submit that they would be at least party

admissions under Federal Rule of Evidence 801(d)(2).

We're aware of the *Kowalski* case which plaintiffs have cited to us. It's an unpublished case from the District of Hawaii which was not applying this court's patent rules.

Obviously these contentions were served under this court's patent rules on defendants. It is far too late for plaintiffs to amend the contentions. These statements were never amended.

We tried to avoid having to move these into evidence by simply adding Amarin's own statements of fact verbatim, a stipulated fact into the Pretrial Order. Amarin refused. It seems they are backing away from these statements that, again, were their own contentions of fact.

Now, you know, we're not arguing they're bound by these contentions as judicial admissions, we would just say that they are at least evidentiary admissions that should come in and FRE 801.

I should just add there are also cases going the other way. We cited one such case from the Eastern District of Texas which hears almost -- many, many patent cases, and that found the other way.

THE COURT: Well, regardless of how other district courts have ruled, I overrule the objection. I find that because the validity contentions were exchanged as part

of the Court's Local Rule, the party that offered the contentions are bound by their contentions and now cannot try to seek to exclude them, therefore, the objection is overruled.

Exhibit 1953 is admitted.

(Defendants' Exhibit 953 received in evidence.)

MR. REIG-PLESSIS: Thank you, Your Honor.

BY MR. REIG-PLESSIS:

Q So turning now to DDX 4.13, there's a snapshot on the screen of DX 1957, page 6. Could you identify this document, please.

A Yes, I can. This is an excerpt from the Karalis paper, ***A Review of Clinical Practice Guidelines For the Management of Hypertriglyceridemia***. It was published in ***Advanced Therapeutics*** in 2017 out of the University of Pennsylvania.

Dr. Karalis goes on to describe in this paper,

"The cornerstone for the treatment of hypertriglyceridemia is lifestyle intervention with diet and exercise."

He goes on further to describe,

"However, pharmacologic therapy to lower triglycerides may be considered based on an individual's cardiovascular risk and how high the level of triglycerides are."

Q So based on Karalis, is pharmacologic therapy to lower

triglycerides in patients with severe -- excuse me -- with hypertriglyceridemia always required?

A No, they are not always required.

MR. REIG-PLESSIS: And, Your Honor, we would move into evidence DX 1957.

MS. KEANE: No objection.

THE COURT: I'm sorry. I didn't hear. Did you say no objection?

MS. KEANE: No objection.

THE COURT: DX 1957 is admitted.

(Defendants' Exhibit 1957 received in evidence.)

MR. REIG-PLESSIS: Thank you, Your Honor.

BY MR. REIG-PLESSIS:

Q So turning to DDX 4.14, Dr. Sheinberg, were you in the courtroom were Mr. Klein presented the testimony on the screen from Dr. Budoff during opening statements?

A Yes, I was.

Q And were you in the courtroom when Dr. Budoff confirmed this testimony during his examination?

A Yes, I was.

Q And how does Dr. Budoff's clinical -- excuse me. How does Dr. Budoff's testimony on DDX 4.14 compare with your own clinical experience?

A Let me first describe what Dr. Budoff is saying here. His -- the question was,

"And so is it consistent with your experience that roughly one-fifth of patients with severe hypertriglyceridemia are able to reduce their triglyceride levels below 500 through diet and exercise alone?"

To which Dr. Budoff replies yes.

And to answer your question after reading that, it is consistent, however, my experience is even more so. Dr. Budoff will say one-fifth of his patients, my experience is it's more closely with -- closer to 70 percent to 75 percent of my patients can reduce their triglycerides below 500 through diet and exercise alone.

Q **And why do you believe your experience differs from Dr. Budoff's?**

A **I can simply tell you that in my practice I see -- there may be several reasons. Number one, we're in different parts of the country so I can only comment on what the dietary makeup for the local central Texas patient population is, which, unfortunately, Texas has a significantly high rate of obesity which is one of the highest in the country.**

Also, the type of patients that I see, I am in a primary setting. In other words, I have -- most of my patients are referred to me by either word-of-mouth, they come in directly, or they come from a primary care physician. I do not have secondary, tertiary referrals.

In other words, I don't work at a large center which specializes or is known to be a research center that would receive more difficult cases.

So I think the combination of my initial patient population -- and, again, I cannot speculate on Dr. Budoff's population or how his practice runs, but I do see quite a bit of individual referrals, patients who do not go through other individuals who are treating their lipids before they come to me.

Q **And is the indicated use of Vascepa to treat severe hypertriglyceridemia limited to patients for secondary or tertiary referrals?**

A **It is not.**

Q **So turning now to DDX 4.15. There's a snapshot on the screen of DX 1960, page 38. Could you identify this document, please.**

A **Yes, I can. This is an excerpt from a textbook on dyslipidemia by Pete Kwiterovich. It is written out of Johns Hopkins, and the chapter 7 which I am quoting here is *Disorders of Hypertriglyceridemia*, written by Dr. Michael Miller.**

It goes on to say that, "in addition to" -- and this abbreviation of HFCS stands for high fructose corn syrup --

> **"A diet high in carbohydrates may lead to an elevation of triglycerides."**

It goes on further towards the bottom and it says, "Regardless of macronutrient intake," which means whether it's protein or fat or carbohydrate, "the most potent manner for reducing triglycerides is through weight reduction,"
which is absolutely consistent with what I see in my clinical practice daily.
Q And do you understand from the testimony earlier today that Michael A. Miller was Amarin's claim construction expert in this case?
A Yes, I do.
Q So turning now to DDX 4.16, there's a snapshot on the screen of DX 1957, page 10.
Now, once a patient starts a triglyceride lowering drug, can it be discontinued?
A Yes, it can.
Q And could you explain.
A Yes, I can. This is an excerpt from that Karalis article that we discussed. The excerpt says,
"If the triglyceride levels fall to normal or borderline level with lifestyle changes and a combination of lipid-lowering therapy, consideration may be given to discontinuing the nonstatin triglyceride-lowering medication."
And then if you look at the bottom of the slide,

there's a simple graphic which represents the initiation of an individual's visit with a physician in which a short course of drug therapy is initiated, along with a lifestyle modification, which again is a diet, reconstruct -- diet construction and an exercise prescription.

That is continued for a brief amount of time, and then the drug can be discontinued when the triglycerides are less than 500 milligrams per deciliter, and we can maintain that with diet and exercise alone.

Q And is the treatment depicted on DDX 4.16 a medically reasonable way to treat a patient with a triglyceride-lowering drug?

A Absolutely.

Q So turning to DDX 4.17, I'll represent to you that this is a snapshot from Amarin's trial brief in this matter which was filed as ECF number 327, at pages 12 and 13, and could you just let us know whether you agree with the statements in this paragraph?

A So in order to give you that answer, I actually have to dissect this paragraph a little bit. That's a little bit more complicated than just answering yes or no because certain things I do agree with, and other things I would like to make a clarification because I do not agree with.

It goes on to say that,

"Severe hypertriglyceridemia is

life-threatening because it puts patients at acute risk of pancreatitis."

I think there's no question. We all agree on that.

It goes on to say,

"It is chronic because it is typically caused by genetic factors."

Well, if we take that portion of this document here, I would argue that it is not chronic and that it is not typically caused by genetic factors. I think my testimony so far has really been evident that the chronicity of this is not something that is definitive. We -- and I've given examples of individuals who can have acute elevations of triglycerides.

When we talk about genetic factors, again, I like to make sure that we delineate the two different types of genetic factors that we're talking about, the absolute discrete genetic abnormality, which is a very small percentage of our patients, versus a genetic predisposition or predilection to develop a problem.

So to say that it is chronic, which is typically caused by genetic factors, I do not believe the way it's written here is correct.

It goes on to say that this cannot be cured through medication, and, again, that sentence or that statement here, we will agree that this type of problem can't

be -- there's no cure.

It's a treatment, not a cure, which is very different than someone who has a pneumonia. In that case, we give medication to cure a pneumonia. Here, we use a treatment.

The problem is the treatment is not necessarily through medication. The treatment, and like I've testified, is really lifestyle limiting.

So, for example -- it's a silly example, but if you have a rowboat that has a hole in it that is filling with water and you keep scooping out the water, you aren't going to get anywhere. You have to fix the underlying problem. You have to patch that hole.

In that example, patching the hole is fixing the underlying lifestyle problem. Unless you fix that problem, you can bail water all day long, and you're never going to have this problem fixed.

The document goes on further to say,

> "If triglyceride-lowering medications are ceased, the severely hypertriglyceridemic patient will have triglyceride levels which will typically rise again to dangerous premedication levels."

And, again, to go back to the example that I said earlier, it's not if the medications are ceased but if the lifestyle modifications are not sustained and prolonged.

This is also manifested in individual patients who yo-yo on their weight.

We take someone who has what we call metabolic syndrome, they're overweight, they're sedentary, they're diabetic or pre-diabetic, we get those individuals well treated, we get them on a diet and exercise program, they lose weight, they are no longer diabetic or pre-diabetic, their blood pressure issues resolve.

If they maintain that, they're great. If they don't, they gain their weight back, they go right back to the same risks they had.

In this case, if they don't maintain the dietary and lifestyle changes that were prescribed, their triglycerides will, again, typically rise to the dangerous levels. But I would argue that it's not the medication that's doing it, it's the lifestyle.

This document further goes on to say,

> **"To prevent triglyceride levels from returning to dangerous pretreatment levels, standard medical practice is to administer triglyceride-lowering medications to severely hypertriglyceridemic patients chronically, not on a short-term, intermittent basis."**

And, again, throughout this example I've laid out several scenarios in which the triglyceride medicine does

not need to be given chronically. It can be given on a short-term basis, and it can be given on an intermittent basis.

To go back to the example that I just mentioned, if I have an individual who was able to effect a good diet and exercise shift, they turn the leaf over, they're exercising, they're not smoking, they're not consuming carbohydrate-rich and sugar-rich foods, that person will have a reduction in their triglycerides.

If that person goes back to their previous lifestyle, their triglycerides will rise. They may now have a need, again, for hypertriglyceride-lowering medicines. They may also have a need again for anti-hypertensive medicines or diabetic medicine.

So all these medicines can be used on a short-term, intermittent basis.

Q Now, do you also have slides on how Vascepa is prescribed in clinical practice?

A Yes, sir, I do.

Q How often do you personally prescribe Vascepa?

A I prescribed Vascepa probably 15 to 20 times per month.

Q Are there similar products that you use more often than Vascepa?

A Yes, there are. I use the -- I use generic version of Lovaza, and I often use over-the-counter fish oil products as

well. There are some over-the-counter products that contain DHA, DPA, and EPA, and some that just contain EPA. So, I use a very similar products on a daily basis in my practice.

Q So turning now to DDX 4.19, there's a snapshot on the screen of DX 2248, page 2, and this exhibit is already in evidence.

When you do use Vascepa, Dr. Sheinberg, what are your main reasons for prescribing it?

A So I will start -- there are several reasons, and let me start with the indications that are listed here from the package insert.

The first indication, which throughout the last two days of testimony we've come to know as the REDUCE-IT indication, which is the indication to reduce the risk of heart attack, stroke, revascularization, which is bypass and stint, and unstable angina, really chest pain requiring hospitalization in the set population which are individuals who have cardiovascular disease or individuals who have diabetes and two more risk factors.

The second indication is an adjunct diet, which is what we've described here as the previous indication, which is to reduce -- or the MARINE indication, which is to reduce triglyceride levels in adults with triglycerides over 500.

But I will also point out there are other reasons which Vascepa is used in my practice, one of which is those of

us who use what we call advanced lipid testing, which is lipid testing or cholesterol testing which doesn't just focus on the amount of cholesterol, we actually focus on the quality of cholesterol.

So, for example, LDL, which is bad cholesterol, occurs in many different sizes. We know these products have an improvement in cholesterol quality.

We also know these products, which is icosapent ethyl, has an improvement in inflammation, and we now understand that when someone has a heart attack, it is actually resulting from an inflammatory change within that artery.

So our understanding of the pathogenesis of heart disease is based on our understanding of the inflammatory changes within the artery. Icosapent ethyl effectively reduces those inflammatory changes which may or may not lead to the benefits that we see here, that's been speculated over and over again.

So the reality is there are multiple reasons to use this medication.

Q Now, just focusing on the two on-label uses of Vascepa, does the REDUCE-IT indication, as the parties have been referring to it, have anything to do with the original MARINE indication?

A They are completely separate indications which affect

completely different patient populations.

I can tell you in my practice of over 400 and some odd patients per month, and, like I said earlier, a patient base of over 25,000 patients, I have rather -- maybe 10, 5 to 10 percent of my patients that will have hypertriglyceridemia to the effect of greater than 500 milligrams per deciliter.

But I will have 70 some odd percent of my patient population which is characterized for the indication for REDUCE-IT. So, they do affect very different patient populations.

Q Now, do the defendants' labels in this case include both of the indications that are on the Vascepa label?

A No, they do not. The defendants' label is consisted only with what we have been categorizing as the MARINE indication, which is the adjunct to diet to reduce triglyceride levels in patients with severe hypertriglyceridemia.

Q And when you prescribe Vascepa for the MARINE indication, do you prescribe it together with diet and exercise?

A Absolutely.

Q And do you generally prescribe Vascepa long-term?

A Generally, I do.

Q And why is that?

A Even though the testimony to follow will show it, and I can tell you in my clinical practice we can see reductions in triglycerides rather rapidly for the effects that I mentioned

previously, which are the reduction of cardiovascular problems which is described above, the improvement in cholesterol quality and particle size and density, and in the anti-inflammatory properties.

If I'm able to get someone on this medication long-term, I would like to use it long term. But the minority of that is to reduce triglycerides in patients over 500 milligrams per deciliter.

Q So is the reason that you keep patients on Vascepa long-term to keep their triglycerides below 500 as required by the MARINE indication?

A Absolutely not.

Q So turning now to DDX 4.20, could you provide an example of how you're able to use Vascepa with a typical patient.

A Yes. This is a slide I put together as an illustrative example. So what it describes here as a first patient visit after undergoing a lipid evaluation.

This individual has a triglycerides of 550 milligrams per deciliter. At the time of the visit, the patient would undergo history, physical exam, other courses of -- or other etiologies that would potentially be contributing to hypertriglyceridemia would be discussed, whether this patient is a smoker, if they're taking medication that could potentially cause this, if they have diabetes, and if they have hypothyroidism. These would be potentially

addressed at that time.

The patient would also be given a specific nutritional plan and a specific exercise plan, either by myself, or I would bring in an exercise physiologist and a nutritionist who I have in my office.

And at the same time, that patient will be given Vascepa or icosapent ethyl specifically because the consequences of pancreatitis are so severe that I want to address those risks absolutely as aggressively and as thoroughly as I possibly can relatively immediately.

After the patient leaves the office, I will have he or she return within a two- to four-month time period. I will have a second set of labs drawn prior to the visit.

In this case the triglycerides have dropped to 300. I'd like to point out the medication and the lifestyle modification has successfully treated the severe hypertriglyceridemic component. Even though this individual is not yet at goal, where I want them, they are no longer in the severe hypertriglyceridemic range, and at that point, a decision is made.

More often than not, I will admit I do continue the Vascepa. It has long-term risk reduction. It has those tremendous benefits on advanced lipidology and advanced lipid testing, and it has a discrete, definitive, anti-inflammatory component.

But, there's a decent proportion of patients at that time that I will discontinue the medication for various reasons, and I will continue to instruct them -- in fact, it is absolutely vital that they continue to make their diet and exercise changes.

Most of the benefit we see in diet and exercise changes do not occur in two to four months, it occurs over a year. So we will continue to see that individual in the clinic, we will continue to measure parameters, but there are people who I will definitively stop this medication for and continue aggressive lifestyle risk reduction.

Q Are there lifestyle interventions that can start benefitting a patient before 12 weeks?

A Absolutely. So we can see discontinuation of smoking, discontinuation of high-sugared beverages, and, again, the reference we keep referring to is alcohol. But, again, where I practice is Dr. Peppers, it's Big Gulps of 64 ounces of a sugared soda, it is gummy bears.

So we can make those differences rather quickly by convincing the individuals to change their habits.

Q Now, have you reviewed any data on how quickly Vascepa can reduce triglycerides below 500?

A Yes, sir, I have.

Q So turning to DDX 4.21. There's snapshot on the screen of DX 1694, page 214, and this is one of the exhibits on the

joint admitted list. Could you identify this document for the record.

A Yes, I can. This is a clinical study report from the MARINE study, and to take you through what we're looking at here, it's the study of icosapent ethyl, and this is a summary of the triglycerides in milligrams per deciliter. Circled is week four, which is the fifth visit of the patient.

You look at the baseline initial evaluation, the average -- I'm sorry, the median triglyceride level at baseline was 679.5 milligrams per deciliter.

If you go down to the week four value, the median has dropped to 471 milligrams per deciliter, and, again, that third drop occurred by week four.

Q So according to Amarin's MARINE study, how long does it take for Vascepa to lower triglycerides below 500?

A Four weeks, and I tell you this is also congruent with what I see in my clinical practice.

Q So turning now to DDX 4.22, there's snapshot on the screen DX 1701, page 68, which is also on the joint list of admitted exhibits.

We've heard some testimony about this document, but could you explain what you're showing on this slide for the record?

A This is the FDA medical review for Vascepa from the Center For Drug Evaluation and Research by the FDA.

This is a -- the paragraph below goes on to say that the open extension MARINE, which was data up to 40 weeks, was submitted as part of the 120-day update.

There is no figure described, but it describes that the maximum triglyceride-lowering effect of 4 grams of Vascepa occurred by week four, and the effects were maintained throughout the study, and, again, this is what we see in the clinical practice world.

Q **So turning to DDX 4.23. There's another snapshot of DX 1701, page 41.**

Did you hear Dr. Budoff's testimony earlier about the sentence "patients with very high triglycerides have a strong genetic component to their decease," and it goes on?

A **Yes, I did.**

Q **What does it mean for severe hypertriglyceridemia to have a strong genetic component?**

A **Again, this is a -- it's a reiteration of what I mentioned little bit earlier, and, that is, there needs to be a definitive delineation here between a genetic abnormality which results in a specific genetic issue and which an individual has no other way around.**

So, for example, if I have an individual who lacks the gene for liposomal protein lipase, lipoprotein lipase, and they have that genetic deficiency, that is a true genetic abnormality.

But even as Dr. Budoff said there are people who don't express think genetic abnormalities completely. There are people who have genetic predispositions or genetic proclivities to have things.

So patients with very high triglycerides levels likely have a genetic component in some way to have elevated -- elevated lipid issues whether it's triglycerides or whatnot.

But it doesn't mean that their genetic differences that we see within the patients make them unable to respond to other interventions such as discontinuation of smoking, engagement in proper exercise -- proper exercise regimens and appropriate diet.

Q **So are genetics the only component contributing to patient severe hypertriglyceridemia?**

A **Absolutely not. Let me take this one step further and definitively argue.**

If I have a patient who's genetically predisposed to be heavy, it may take us a little bit more dietary coaching or a little bit more exercise prescription to get that person where they need to be, but it doesn't mean it can't be done. In fact, we do every single day.

Q **So does everyone with a genetic predisposition for severe hypertriglyceridemia require drug treatment?**

A **No, they do not.**

Q **So turning now to DDX 4.24, there's another snapshot of DX 1701, page 41, which is still on the screen, and before I get to the slide, what is your goal for triglycerides in terms of the patients you treat?**

A **Ultimately I like to try to shoot for a triglyceride level which is less than 150 milligrams per deciliter.**

Q **And are those normal triglycerides?**

A **That would be considered normal.**

Q **At what point does the FDA consider therapy with Vascepa successful?**

A **They consider therapy successful in this population if the triglycerides are lowered to less than 500 milligrams per deciliter.**

Q **And does it take 12 weeks to achieve that success for purposes of the indicated use?**

A **It does not.**

Q **Now, does Vascepa successfully reduce triglycerides in all patients?**

A **It does not.**

Q **So turning to DDX 4.25, there's snapshot on the screen of DX 1694, page 12, which we reviewed earlier.**

According to the MARINE study report, are there patients on Vascepa who do not experience triglyceride reductions?

A **Yes, that is correct. To look at this document, this is**

an excerpt from the Amarin MARINE study, the Clinical Study Report.

What we're look at here which is highlighted is the percentage change from baseline to the 12-week evaluation. It's the endpoint in fasting triglycerides, and you can see at the bottom which highlighted, percent change from baseline, the median is 26.6 percent.

But if you look at what is described at Q1 and Q3, Q1 is the median in the first half of the group receiving this medication, the Q3 designation is the median of the second half of the group receiving this medication.

And you can see the median of that second half absolutely had a 0.0 percent change which means there are some people in this evaluation who actually had an increase in triglycerides, up to 25 percent of those people based on what we see here.

Q Does the MARINE Clinical Study Report also include data on LDL-C and apo B levels?

A Yes, it does.

Q So turning to DDX 4.26, there's a snapshot on the screen now DX 1694, page 268. According to the MARINE study report -- I'm sorry.

Are there patients taking Vascepa who's LDL-C increases according to the Clinical Study Report?

A Yes, this is the same type of data we just looked at on

the previous analysis. This is percent change in LDL from baseline to week 12.

And you can see, although there was median reduction of 4.5 percent, if you look at Q3, which is the median of the second half of the data group, there was an increase in LDL-C of 17.2, which means, again, that's the median, so there's a group of people in this evaluation who had an LDL increase above 17.2 percent.

Q And turning now to DDX 4.27, there's snapshot on the screen of DX 1694, page 239. Are there patients taking Vascepa whose apo B is not reduced?

A Yes, that is correct. Again, same document. It's laid out in the same way. This time we're looking apolipoprotein B.

Their percent change from baseline, the median was a reduction of 3.8 percent. But, again, if you look at that Q3 evaluation highlighted in yellow, you can see in that second half of the group that there was an actual 3.8 percent rise in apolipoprotein B which again indicates that are certain individuals, up to 25 percent, who had a rise which was even higher than 3.8 percent.

Q So turning to DDX 4.28, there are snapshots on the screen of DX 2248, DX 2256, and DX 2266. Could you identify these documents for the record.

A These are the package inserts or the labels for Vascepa

for Hikma's icosapent ethyl and Dr. Reddy's Laboratories' icosapent ethyl.

MR. REIG-PLESSIS: And I believe DX 2248 and 2256 are already admitted, but we would move into evidence DX 2266, which is the DRL label.

MS. KEANE: No objection, Your Honor.

THE COURT: 2248 is admitted.

MR. REIG-PLESSIS: And, I'm sorry, it was 2266. I believe 2248 --

THE COURT: I'm sorry -- I looked at the first one, 2248, 2256, 2266 are the three that are laid side by side?

MR. REIG-PLESSIS: Correct, Your Honor. I believe the first two --

THE COURT: I thought all of them were admitted already. All the labels are in, aren't they?

THE CLERK: One was not, two was, 2266, Your Honor.

THE COURT: The DRL label is not -- well, if it hasn't been, it will be admitted.

(Defendants' Exhibit 2266 received in evidence.)

MR. REIG-PLESSIS: Thank you, Your Honor.

I believe perhaps the PX version was previously admitted, so we're moving into evidence just the 2266 DX version.

THE COURT: Thank you.

MR. REIG-PLESSIS: Thank you.

BY MR. REIG-PLESSIS:

Q Dr. Sheinberg, are any differences between these three labels, the Vascepa label, the Hikma label, and the DRL label, material to any of your opinions relating to infringement of the asserted claims?

A There is no difference.

THE COURT: I'm sorry, what was the answer?

THE WITNESS: I'm sorry, would you ask the question again? I want to make sure I answer it properly.

MR. REIG-PLESSIS: Sure.

BY MR. REIG-PLESSIS:

Q Are there any material differences between the Vascepa label, the Hikma label, and the DRL label, and when I mean material, I mean differences that are material to your noninfringement opinions.

A There's no difference, no material difference.

Q Are any differences between the Vascepa product and defendants' generic products material to your opinions?

A No.

Q So let's move on to your noninfringement opinions. What topics do you tend to address in your analysis?

A Well, now that we've finished the background, my noninfringement analysis will effectively cover three

different topics, the 12 weeks duration topic, the lipid effects topic, and the no concurrent lipid-altering therapy topic.

Q What is the legal standard that you applied in analyzing defendants' labels?

A The legal standard that I used is, quote,

"In order to induce infringement, the label must encourage, recommend, or promote infringement. Merely describing an infringing mode is not the same as recommending, encouraging, or promoting an infringing use, or suggesting that an infringing use should be performed."

Q Now, just to be clear, Dr. Sheinberg, are you a lawyer?

A No, I am not.

Q Are you offering any legal opinions?

A No, sir, I am not.

Q Are you offering any opinions on FDA regulatory issues?

A No, sir, I am not.

Q Are you offering opinions from the perspective of a physician?

A Yes, I am.

Q Now, as a physician, what parts of a drug label do you generally expect to provide instructions on the duration of treatment for a drug?

A Typically the areas that provide instruction are the

indication and usage and the dosage and administration sections of the package insert.

Q So turning to DDX 4.31, there's snapshot on the screen from DX 2256, pages 1 and 2. What are you showing on this slide?

A This is the indication and usage section of the package insert of defendants' label, and it goes on to describe icosapent ethyl as indicated as an adjunct to diet to reduce triglyceride levels in patients with severe hypertriglyceridemia.

Q Now, to a physician, does the term severe hypertriglyceridemia in the indication imply that indefinite drug treatment is required?

A Absolutely not.

Q Is the indication for defendants' products limited to patients with a genetic abnormality?

A It is not limited to any patient of any type.

Q So are the indicated uses for defendants' products limited to chronic use?

A No, they are not.

Q And according to the indication, are defendants' products a primary treatment for severe hypertriglyceridemia?

A They are not. They're adjunctive therapy which means they need to be used in combination with diet.

Q So does the indications and usage section encourage

recommend or promote administering defendants' products for at least 12 weeks?
A No, it does not.
Q Now, turning to DDX 4.32, were you in the courtroom when Mr. Klein presented the testimony on this demonstrative from Dr. Budoff during opening statements?
A Yes, I was.
Q And were you in the courtroom when Dr. Budoff confirmed that testimony?
A Yes, I was.
Q And is your opinion consistent with Dr. Budoff's testimony on this point?
A Yes, and to describe it, Dr. Budoff was asked and do you agree it would still be consistent with the Vascepa labeling for a doctor to prescribe Vascepa for fewer than 12 weeks, to which Dr. Budoff replied yes.
Q Turning now to DDX 4.33. There's snapshot on the screen of DX 2256, page 2. What are you showing on this slide?
A This is the dosage and administration section of the package insert of defendants' drug, and under section 2.1 it really goes on to describe what we've been talking about which is obviously prior to initiation of icosapent ethyl assess lipid levels which it's obvious, identify other causes which we have talked about, and manage as appropriate, which I testified earlier that would include treatment of those other

issues concomitantly with the use of lifestyle therapy and medication.

It goes on as second bullet to say patients should engage in appropriate nutritional intake and physical activity before receiving icosapent ethyl which should continue during treatment with icosapent ethyl.

Q Does the instruction to identify and manage other cases imply that medication should be delayed until those causes are addressed?

A Absolutely not. It's giving me sort of a direction that we need to fix underlying causes as appropriate, but it does not state that that should be done specifically prior.

And I would argue specifically against doing that because we understand the severe consequences in morbidity and mortality for pancreatitis, that we want to treat that as aggressively as we possibly can.

Q So focusing now on the second bullet under section 2.1, does the statement to engage in nutritional intake and physical activity before receiving icosapent ethyl mean that a patient should wait for diet and exercise to take effect before icosapent is administered?

A It's my interpretation of this that that is not the case. Again, ultimately, a goal for the prescribing physician is to make sure we keep our patients healthy and out of the hospital. In order to do so in this case, we have to keep

those people from developing pancreatitis.

So in terms of engaging in appropriate nutritional intake and physical activity, it does not specifically describe how long that should be, what it should be, and that's really up to the discretion of the prescribing physician.

I interpret this unequivocally to mean I have to make the appropriate nutritional and physical activity assessment and recommendations and then, in the same visit, prescribe the medication.

For example, if I have an individual who is a smoker, and I tell that individual after sitting with them and counseling them and showing them the risks, and I said to that individual, "I need you to stop smoking," and they say, "Okay, Doc, I understand, I'm going to stop smoking," well, that was a successful intervention right there. He immediately is engaged in appropriate smoking cessation.

The same thing holds true with alcohol consumption, or the example that I've been using this afternoon was the Dr. Pepper, and this is Texas where I grew up so Dr. Peppers are the thing out there, but it could be substituted for anything else.

But I can tell an individual, you know what, those Big Gulps of Dr. Pepper that you're drinking every day, it's not helping, in fact, that's causing your problem. The

patient can turn around say, "Okay, I understand, I'm done with Dr. Peppers." Well, we just -- that patient just engaged in appropriate nutritional effect.

Same thing goes physical with activity. It's January 1st, the gyms are filled with people who, on January 1st, are starting a physical activity program. They may join a gym, they've engaged in physical activity.

So it's really at the discretion and interpretation of the physician and how this sentence is actively utilized.

Q In your practice, do you delay administering drug therapy when a patient presents with severe hypertriglyceridemia?

A I don't. I can't. In fact, I would argue along those lines that if I have a patient that comes to my office with severe hypertriglyceridemia, and I don't treat it aggressively to the best of my ability, and that individual leaves my office just to come back in four to six weeks for reassessment, and they develop acute pancreatitis within those four to six weeks, I feel that I have violated the standard of care, that my colleagues would look at that and say why didn't you treat this person when he was in your office.

Because the consequences are so severe, every possible avenue of therapy needs to be addressed immediately at that first visit.

Q So, in your opinion, is it an off-label use of Vascepa to start Vascepa and diet and exercise at the same time?

A **It is not.**
Q **So turning now to DDX 4.34, were you in the courtroom when Mr. Klein presented this deposition testimony from Dr. Budoff during opening statements?**
A **Yes, I was.**
Q **And were you in the courtroom when Dr. Budoff confirmed this testimony?**
A **Yes, I was.**
Q **Is your opinion consistent with Dr. Budoff's testimony on this point?**
A **Yes. And, actually, again, let me read it into the record.**

Dr. Budoff was asked,

"The dosage and administration section in the Vascepa label leaves it entirely up to the physician's discretion to determine the duration of treatment. Do you agree?"

To which Dr. Budoff replied yes.

And, again, that is my understanding, and I do agree that it is entirely up to the physician's discretion.

Q **And just to turn back to DDX 4.33 for a moment, does the reference to engaging in appropriate nutritional intake require the patient to eat specific foods, or would it also include restraining from eating certain foods?**
A **It really is a combination of both, and it has to be**

addressed on a specific individual level, which takes into consideration where that person is in terms of their lifestyle, if there's any predisposing ethnic issues which would predispose that individual to eat in certain different food groups, if that person is a vegetarian, if they have other dietary restrictions.

So it does not describe in any way, shape, or form what that nutritional intake change should be here. It simply tells me it needs to be what is described as, quote, appropriate, unquote.

Q So in your example would ceasing to consume Big Gulps of Dr. Pepper be engaging in appropriate nutritional intake or be one component of that?

A Absolutely.

Q Now, have you compared defendants' labels to labels for other drugs that actually specify duration of treatment?

A Yes, I have.

Q So turning first to DDX 4.35, there's a snapshot on the screen of DX 1984, page 2. Could you identify this document.

A Yes, I can. This is the Lamisil label. Lamisil is an antifungal tablet which we use for fingernail and toenail infections, fungal infections.

MR. REIG-PLESSIS: And defendants would move in the admission DX 1984.

MS. KEANE: No objection, your Honor.

THE COURT: DX 1984 is admitted.

(Defendants' Exhibit 1984 received in evidence.)

BY MR. REIG-PLESSIS:

Q How does the dosage and administration section of the Lamisil label compare to the same section in defendants' labels?

A It's discretely different.

The Lamisil label goes on to specifically prescribe a duration of therapy which is in complete contradistinction to what is seen in the defendants' label, for example, for fingernail onychomycosis which is a fingernail infection.

It specifically directs me to have the individual use one tablet once daily for six weeks. For toenail infections, it specifically instructs me to have an individual take one tablet once daily for 12 weeks.

Q Have you ever prescribe Lamisil?

A Yes, I have.

Q So turning to DDX 4.36, there is a snapshot on the screen of DX 1679 at page 5. Could you identify this document, please.

A Yes, this is the dosage and administration section for the package insert of what's called Lovenox which is enoxaparin. It's an injectable low molecular heparin or an injectable blood thinner.

In this case, they're describing the use of this

drug in the treatment of deep venous -- deep vein thrombosis which is a clot with or without pulmonary embolism which is a clot in the lungs.

The label goes on to specifically describe and instruct the physician to initiate Warfarin which is Coumadin, it's an oral blood thinner, when appropriate, and then continue Lovenox for a minimum of five days and until a therapeutic anticoagulant effect has been reach on the Coumadin.

So, again, in complete contradistinction to defendants' label, this label instructs a providing physician to use this medication for a minimum duration of time that's specifically spelled out.

MR. REIG-PLESSIS: Defendants' move the admission DX 1679.

THE COURT: Isn't there already the Lovenox label admitted earlier?

MR. REIG-PLESSIS: Your Honor --

THE COURT: Regardless, is there objection?

MS. KEANE: No objection.

THE COURT: All right. DX 1679 is admitted.

(Defendants' Exhibit 1679 received in evidence.)

MR. REIG-PLESSIS: Thank you, your Honor.

And I believe some of the PX exhibits and DX exhibits refer to the same documents because these

demonstratives were prepared before we knew what they would admit.

THE COURT: All right. I remember Dr. Budoff testifying as to the Lovenox label I think.

MR. REIG-PLESSIS: Thank you, your Honor.

BY MR. REIG-PLESSIS:

Q Turning now to DDX 4.37, there's snapshot on the screen of DX 2256, page 7. What are you showing on this slide?

A This is the clinical study section of the defendants' package insert or label in the clinical study section which is described in 14.2 severe hypertriglyceridemia.

There's a reference to what we've described today as the MARINE study, and I have highlighted here,

"Patients whose baseline triglyceride levels were between 500 and 2,000 were enrolled in the study which went on for 12 weeks in duration."

Q So does the clinical study section describe the use of EPA for 12 weeks?

A It describes the use of EPA in this study for 12 weeks.

Q In your practice as a physician, do you look to the clinical study section of a drug label for instructions on how long to administer that drug?

A I do not. I look at the clinical studies section so I can understand the rationale for using this.

It's simply -- what is described here is a simply a

discussion and a synopsis of what was seen in the reference trial.

Q To a physician, does the statement that the clinical trial lasted 12 weeks indicate that patients need to be treated for at least 12 weeks to reduce their triglycerides below 500?

A Absolutely not. It does not describe that or encourage that. It simply describes what was found in the study.

You can go further on to say, you know, if you look at the MARINE study, most of the individuals in the MARINE study were 53-year-old white males which doesn't correspond to the majority of my patient population anyway. So it's hard to extrapolate.

The only thing this description tells me is what was done in the MARINE trial.

Q So does the clinical study section encourage, recommend, or promote administering defendants' products for at least 12 weeks?

A No, sir, it does not.

Q So turning now to DDX 4.38, there are snapshots on the screen again of DX 2256, but now at pages 3 and 5. Are there any other references to a 12-week duration in defendants' drug labels?

A Yes, there are.

In section 6, which is the adverse reaction section,

they describe two randomized, double-blind, placebo-controlled trials in patients with triglycerides between 200 and 2,000 who were treated for 12 weeks, and it describes the adverse reactions that occur.

And in the second section, which is the clinical pharmacology section under the pharmacodynamic subheading, it describes a 12-week dose-ranging study in patients with severe hypertriglyceridemia, and it describes it that it reduced the triglycerides from baseline to placebo.

Q And, in your opinion, do these descriptions of a 12-week duration encourage, recommend, or promote administering defendants' products for at least 12 weeks?

A Again, absolutely not. This 12-week reference simply describes in the first case two randomized studies that were done looking at adverse reactions, and, in the second section, it describes a dose-ranging study to show that there was reduction in triglycerides relative to placebo.

But, again, these 12-week durations simply describe what was seen in these limited studies, it does not in any way indicate to me that that is how long I need to treat my patients for.

Q So turning now to DDX 4.39, there's a snapshot on the screen of DX 2256, page 9, and it's a snapshot from the patient information section of defendants' labels.

Do you see the statement, "Do not change your dose

or stop taking icosapent ethyl without talking to your doctor"?

A Yes, I do.

Q In your opinion, does that statement encourage, recommend, or promote administering defendants' products for at least 12 weeks?

A It does not. It simply instructs the patients to take the medication that has been prescribed in the way it's been given to you. Do not alter the medication without discussing it with your own physician.

Q When a patient talks to his or her doctor, could the doctor tell the patient to take the drug for less than 12 weeks?

A Absolutely. I receive at least a dozen phone calls a day from patients, most of which are medication issues that need to be resolved.

Often times after talking to the patient, I will agree to stop that patient's medication well below the 12-week limit or 12-week prescription.

Q And you may have testified to this before, but after prescribing a drug like Vascepa to a patient, how long do you usually wait before seeing that patient again?

A Anywhere between two and four months would be very reasonable in my practice.

Q So do you sometimes see patients again before 12 weeks?

A **Very frequently.**

Q **And have you told patients that it's okay to stop Vascepa?**

A **I have.**

Q **And what are some of the reasons why a patient may want to stop Vascepa?**

A **Well, if I have someone who has had a very successful change in lifestyle, in other words, they're adhering to the exercise prescription and nutritional recommendations that we've made, we will stop the Vascepa because at this point, they no longer need it.**

There are also other reasons. Individuals can't afford it. Some individuals have side effects. My experience with this medication has been mostly GI or gastrointestinal side effects. There are people who are eager to get off all medications. So it is not infrequent that we stop medications for these patients.

Q **Is the size or number of pills a contributing factor in patients' decisions?**

A **Without question. This is a difficult medicine to take because it's a large number of pills, it's four pills. If you've never seen these pills, patients joke and say they're horse capsules, they're very large capsules, and there's a lot of people that cannot swallow these capsules and simply because of that reason want to stop their medication.**

Q **Now, on the screen is DDX 4.40 with another highlighted snapshot of the same page, DX 2256, page 9.**

Does the patient information section suggest any other treatments for reducing triglycerides?

A **Yes, it does. It says, "Your doctor may start you on a diet." It specifies what potential type of diet that would be, and it specifically says "stay on this diet while taking this medication."**

Q **So turning now to DDX 4.41, there's a snapshot on the screen of DX 2256, page 10.**

If a physician decides to administer defendants' products long-term, is that necessarily for the indicated MARINE use of treating patients with triglycerides of at least 500?

A **It's not. I testified earlier during this testimony that oftentimes we use this -- most often we use this medication for other reasons than the MARINE data, and in the patient information section it specifically tells the patients that we would potentially do that.**

It describes a situation in which medicines are sometimes prescribed for purposes other than those listed in the patient information leaflet.

Now, as a prescribing physician I like to think we would talk to the patient and explain the reasons why, but this gives us full latitude in which in order to do so.

Q So taking defendants labels as a whole, do the labels encourage, recommend, or promote administering defendants' for at least 12 weeks?

A I'm sorry, can you repeat that one more time so I make sure I answer the question properly?

Q Sure. Taking defendants' labels as a whole, do the labels encourage, recommend, of promote administering defendants' products for at least 12 weeks?

A No, they do not.

Q Do they express any preference for short-term versus long-term use?

A The labels are completely silent in this regard, and therefore and it is left up the discretion of the prescribing physician.

Q What is the next set of claim limitations that you analyzed?

THE COURT: Mr. Reig, how much longer do you have for Dr. Sheinberg's direct examination?

MR. REIG-PLESSIS: Probably 15 more slides. We've covered obviously the 12 weeks duration, but there are two other categories of limitations.

THE COURT: I'm trying to assess whether it makes sense to recess the testimony portion for today.

If you had about five minutes or so, I would let you continue and then have plaintiffs start with the

cross-examination in the morning, but if you think you have longer than five to ten minutes, I would probably pause and recess for the day.

MR. REIG-PLESSIS: I would estimate that we have probably little more than that, so a recess might make sense, Your Honor.

THE COURT: We'll at least pause the testimony portion for today. I want to have enough time to give you my ruling on the Rule 52 motion earlier. So, at this time, let's do that.

I'm going to ask Dr. Sheinberg to step down from the witness stand.

THE WITNESS: Yes, your Honor.

THE COURT: And then we'll resume with your testimony in the morning. I understand you have patients to see, but, unfortunately, you have to return tomorrow.

THE WITNESS: That's okay.

MR. REIG-PLESSIS: Thank you, Your Honor.

THE COURT: All right. I will try to speak slowly lest I get an instruction to slow down.

Here's my ruling on the Rule 52 motion.

Defendants asked for judgment under Rule 52(c) as to plaintiff's induced infringement claim based on the claim limitation presented in all of the asserted claims that is requiring the administration of EPA for at least 12 weeks.

However, I will not enter judgment in defendants' favor at this time because I find that plaintiffs present sufficient evidence to satisfy the preponderance of the evidence standard as to the 12-week limitation.

The question of whether defendants may be held liable for inducing infringement turns on whether defendants have, and I quote from the *Grunenthal* decision, this is at 919 F.3d 1333 at 1339, it's a Federal Circuit 2019 decision, and, that is, defendants have -- the issue turns on whether defendants have specific intent based on the contents of their proposed labels to encourage physicians to use their proposed ANDA products in a way that infringes the asserted claims.

In other words, I have to find -- I have to ask whether the label, and I quote, encourages, recommends, or promotes infringement. These are the terms that counsel have used extensively throughout the examination and cross-examination, and the PIN cite for that is the same, it's at 1339.

And because the asserted claims are method claims, I quote again, the pertinent question is whether the proposed label instructs users to perform the patent method, and the pin cite is the same at 1339.

Defendants' primary argue that their proposed labels cannot be read to encourage, recommend, or promote infringement of the 12-week limitation. However, Dr. Budoff

testified that reading the label as a whole, physicians would be encourage to prescribe Vascepa or one of defendants' ANDA drugs, the labels that are materially the same, for at least 12 weeks.

He testified that this is because a clinician working in the field would know that STG, severe hypertriglyceridemia, is largely a genetic problem requiring long-term therapy.

Moreover, on cross-examination, Dr. Budoff testified that STG is almost invariably a chronic condition. He also testified to his own treatment practices describing that he almost always prescribes Vascepa for more than 12 weeks and checks in with his patients about every three months to monitor their lipid levels over the long term.

He also points to portions of the labeling supporting his testimony that the proposed labels encourage infringement of the 12-week limitation.

He specifically pointed to section 2.1 of the labeling, and I'll refer to PX 1186, as I say, the labels are the same, that is the December 2019 Amarin's label for Vascepa.

He points to section 2.1 regarding what a doctor needs do before initiating therapy with Vascepa. He testified that this section of the labeling supports his testimony that drug therapy using Vascepa is intended to be long-term. He

emphasized how the labeling tells doctors to first identify other causes of STG and manage them as appropriate before initiating therapy.

Therefore, a doctor would not begin Vascepa therapy if the doctor can identify and remediate those other causes such as diabetes.

Second, he testified that the labeling instructs doctors to encourage patients to change their diet and get more exercise before Initiating drug therapy. So he read the labeling to require elimination of acute causes before initiating Vascepa.

In other words, Dr. Budoff testified that the only people left after removing the groups of people suffering from acute causes of STG are people who have the genetic disorder causing their elevated STG levels, and that is a lifetime problem so doctors would initiate long-term therapy for this chronic condition.

Now, defendants point to excerpts from Dr. Budoff's testimony to argue that STG is not a chronic condition, and on cross-examination Dr. Budoff acknowledged that binge drinking, for example, can cause a spike in the TG levels to over 500 milligrams per deciliter in patients who are predisposed to high TG levels, and these patients can get their TG levels back below 500 by cutting out alcohol if their TG levels were sufficiently close to 500.

But he also explained that people who eat too much or drink too much without an underlying medical issue would not have STG, and, again, he explained that the label instructs physicians to eliminate these acute cases first.

For those reasons I find that plaintiffs have at least met their initial burden such that defendants are not entitled to judgment of noninfringement on plaintiff's induced infringement theory at this time, and the Rule 52(c) motion is denied.

All right. With that we'll resume in the morning at 8:30.

THE CLERK: Your Honor, may I ask clarification please? I have not filed the minutes of yesterday yet because of a question of a chart that may be produced by counsel with regard to Mr. Klein's cross-examination. Should I go ahead and submit my minutes as they are written?

THE COURT: Why don't you submit the minutes, and the chart that will be created, counsel can file that on the docket.

There is -- I probably should resolve the evidentiary issue raised at the end of yesterday about the 25 additional exhibits. I don't know if counsel -- Mr. Rounds, if you have identified which expert or which documents will be used with which expert because I don't know if they'll up tomorrow.

MR. ROUNDS: Yes, we did that last night, your Honor, and, no, they're not up tomorrow.

THE COURT: Will they be up Friday?

MR. ROUNDS: No, not as far as I know.

THE COURT: Well, I've looked at the exhibits, and my preliminary reaction is I don't think that it supports the -- while I realize that there are -- well, let me describe what the exhibits are. Give me one moment.

So there were 25 exhibits and they're various categories and they are exhibits that were produced by Amarin. I think they're about 136 pages, although there were a few blank pages. They include the drafting labeling for the EPA capsules, there's an article by an Amarin employee about the MARINE and the ANCHOR studies, 1099 tax forms for a company, some e-mail exchanges, the CV of Edward A. Fisher, I assume he's one the witnesses.

My point is, while I agree with Amarin that deadlines are there for a reason, they're -- they're there to ensure fair play and that there's no ambushing of any of the attorneys or counsel at trial -- or the witnesses at trial, so I expect -- and I'm very rule-oriented person. I expect counsel to follow the rules.

But I do understand that given the voluminous nature of the exhibits in this case, and the complexities of the testimony of the witnesses, that -- such that I will

accept the explanation for the delay in identifying these additional exhibits.

And because of the volume, because of the fact that they were documents produced by Amarin, I don't -- I'm not persuaded by the argument that there's prejudice to Amarin if I don't exclude the additional exhibits, and that's the main reason why I'm going to permit the exhibits to be offered. Whether or not individually they will be admitted at trial is a different issue, but I'm not going to exclude them for their late disclosure.

Therefore the motion that was filed orally yesterday to exclude the additional 25 exhibits is denied.

I expect going forward that counsel will comply with the rules. I know that you're updating your exhibit lists constantly, and I understand that there's fluctuations during the trial. Peggie has probably already reminded you that when you do that, you need to give me the updated exhibits and the updated exhibit list.

Okay. With that we'll resume in the morning.

(The evening recess was taken.)

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I certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter.

/s/ Kathryn M. French

1/25/2020

Kathyrn M. French, CCR #392, RPR **Date**

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