UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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GENE COMPANY PTY LTD.

Petitioner,

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY

IN THE CITY OF NEW YORK,

Patent Owner.

_____

IPR2024-00313

U.S. Patent No. RE47,045

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GENE COMPANY - EXHIBIT 1069 - Gene Company PTY LTD, v.
The Trustees of Columbia University in the City of New York - IPR2024-00313

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(Deposition commenced at 9:06 a.m.)

LUCIANO "LUCIAN" VITO DEL PRIORE, M.D., Ph.D., being first duly sworn and/or affirmed, was examined and testified on his oath as follows:

THE REPORTER: Please state your full name for the record.

THE WITNESS: My first name is Luciano, L-u-c-i-a-n-o, middle name is Vito, V-i-t-o, and last name is Del Priore, D-e-l P-r-i-o-r-e. I go by "Lucian" usually.

EXAMINATION

BY MR. MILLS:

Q. Thank you, doctor. Please go ahead and tell us your correspondence address as well.

**A. My professional work address is 40 Chapel Street, Suite 1B, New Haven, Connecticut, 06520.**

Q. Have you ever been deposed before?

**A. Yes, I have.**

Q. Approximately how many times?

**A. Five or six.**

Q. Just for formalities and to keep everything in order, I want to talk just about some

rules of deposition, which are probably familiar to you from your prior experience.

So the first one is that the record of the deposition is a transcript that the court reporter is taking down, so it's important that no one in the room, the attorneys or you, speaks at the same time as another person.

Does that make sense?

**A. Yes, it does.**

Q. Okay. It's also important that all of the answers that you give to the questions today be audible so the court reporter can write them down.

Does that also make sense?

**A. Yes, it does.**

Q. If at any time you don't understand the question that I'm asking you, will you let me know so that I can make sure the record is clear?

**A. I understand that. Thank you.**

Q. The attorney sitting next to you at times might raise objections. Unless you are instructed not to answer the question, you still need to answer the question.

Do you understand that?

**A. Yes.**

Q. And you understand that you are under

oath today the same way as if you were in court in front of a judge and a jury?

**A. Yes, I do.**

Q. When was the last time that you were deposed?

**A. The last time I was deposed was approximately two years ago.**

Q. What was the general subject matter of that case?

**A. It was a patent case. I've done depositions for medical-legal also, but that was a patent case.**

Q. Approximately how many patent cases have you been involved in as an expert?

**A. Maybe five.**

Q. Of those five patent cases in which you've been an expert, how many of those were you testifying on behalf of the patent owner?

**A. I would have to think about that. I honestly don't recall. But I -- I honestly don't recall.**

Q. Can I have your best estimate?

**A. I'd have to think about the individual cases which will just take me a moment. Defendant, probably 80 percent of the time maybe. I can think**

**of one that's the other way.**

Q. And when you say "defendant," you mean the person challenging the patent?

**A. No, the person holding the patent.**

Q. Okay.

**A. Apologies.**

Q. That's okay. So approximately, your best estimate is about four of the five patent cases in which you've been an expert, you were offering testimony on behalf of the owner of the patent?

**A. That is correct.**

Q. Of those five patent cases, did any of them have anything to do with vitamin A?

**A. No, not to my recollection.**

Q. Did any of them have anything to do with a deuterated compound?

**A. No.**

Q. In a general medical or scientific nomenclature, what was the subject matter of your most recent patent case?

MR. FELDSTEIN: And, doctor, I just advise you that to the extent you have confidential information from other cases, that you may be under obligation not to disclose that, and I don't think that counsel is asking you for confidential

information.

THE WITNESS: Okay. Thank you.

Generally, one of them -- the most recent one was related to patent litigation about a compound that was in a chemical class of anti-VEGF compounds. VEGF stands for vascular endothelial growth factor, so that was the subject matter of the most recent one.

Q. And that particular active ingredient was used to treat what?

**A. That particular active ingredient is used to treat a variety of things. It's used to treat cancers, which is outside of my field of expertise, and it's used to treat exudative or wet macular degeneration.**

Q. Now I have the same question about the next most recent case. What generally was the subject matter of that?

**A. The subject matter of that case -- let me give this some thought for a moment. Essentially it was related to the way molecules in the back of the eye attach to their basement membrane. So the molecules in the back of the eye are not free-floating like your blood. They are actually -- they are actually stuck to a surface**

**like your kitchen tiles are stuck to the subfloor underneath it. And with cells, there is actually a molecular mechanism by which the tiles are adhering to the subfloor, and that was the general idea of that patent.**

Q. And you said molecules, and you also said cells attaching. So can you clarify for me?

**A. Of course, of course. So the cells, in the kitchen tile analogy, the cells will be the tiles. They are relatively large by cell -- you know, for ophthalmologists, I guess, they are about 100th of a millimeter in size. And then the molecules are the proteins that are present on the surface of the cells that will adhere them to the bottom layer.**

Q. What type of cells are at issue?

**A. These particular cells were the retinal pigment epithelium, which is the layer underneath the retina.**

Q. And if we refer to those as "RPE cells," will that make sense to you?

**A. Yes, perfectly.**

Q. Great. Now I have the same question about the next further back case, if you can recall back that far.

**A. Okay. Just give me a minute to give that some thought, if you don't mind. It would have been more than 10 years ago probably, so I don't remember the specifics of it. It did not get to the deposition stage. It was preliminary review of material on behalf of a patent that an attorney asked me my professional opinion on it.**

Q. Now, I have the same question about the next further back case, if you can recall that one.

**A. I don't recall. I'd really have to go through my files to be able to answer that.**

Q. Just for completeness, I'll ask about the fifth and final patent case in which you were an expert.

**A. Same answer, it was pretty far back in time.**

Q. Now my question is: Outside of the realm of being an expert, have you been involved in any patent cases?

**A. Can you clarify the content that you're --**

Q. Let me ask you a more specific question: So have you been a witness in a patent case in which you were not serving as an expert?

**A. No, I have not.**

Q. Have you been involved in a patent case from the perspective of having an interest yourself in a patent?

**A. I have patents myself, but I have not been involved in a case regarding one of my own patents.**

Q. And is there some other involvement that you've had in a patent case in which you were not participating as an expert?

**A. No. Not to my knowledge.**

Q. You mentioned that you have some patents on which you are the inventor?

**A. Yes.**

Q. Have you licensed those patents to any companies?

MR. FELDSTEIN: And, doctor, I don't think he's asking you for confidential information.

THE WITNESS: I'm sorry?

MR. FELDSTEIN: I don't think he's asking you for business confidential information. Nothing here -- everything here is on the public record.

THE WITNESS: Okay.

Q. So let's start with public information. If there is confidential information, without going

into it, you can just tell me, and in addition to that, there is confidential information, and we can decide where to go from there.

**A. Okay. Great. Can you repeat the question?**

Q. Yes. So are there any companies to which you have licensed any of the patents that you own?

**A. We're in the process of licensing a patent from the university that I'm one of the coauthors on, to a biotechnology company but I'm also a founder of.**

Q. Can you tell me the name of that company?

**A. Tell you --**

Q. The name of that company on which you --

**A. The name of the company is F-e-r-r-x, Bio, Ferrx Bio.**

Q. Do you know what Bain Capital is?

**A. Yes. I've heard of Bain Capital.**

Q. Is Bain Capital involved in the funding of Ferrx Bio?

MR. FELDSTEIN: Doctor, you are not obliged to provide him confidential information on your businesses. This is beyond the scope so I object. You are not obliged to give your business confidential information.

THE WITNESS: Okay. Should I answer the question?

MR. FELDSTEIN: You are not obliged to give him confidential information about your business.

THE WITNESS: So non-confidential information, we are just reaching out to investors now, and there are many venture capital firms on that list.

BY MR. MILLS:

Q. I'm not trying to make you feel uncomfortable. Just for the record, I disagree with counsel. There isn't any rule that says I can't ask you about confidential information, but I'm not trying to make you uncomfortable. I'm just trying to find out if you have a relationship with the funders of the party in interest here.

So let me ask another foundational question: Do you have an understanding that Bain Capital is a major investor in -- actually, let me start with an earlier question.

Do you know who Alkeus is?

**A. I know who Alkeus is, yes.**

Q. What is your understanding in a general sense as to what Alkeus is?

**A. Alkeus is a biotechnology company, privately held at this point, that essentially has taken at least one compound, ALK-001, that has received tranches of funding that has allowed them to embark on early clinical trials of their compound.**

Q. And you understand that Alkeus is a real party in interest as an exclusive licensee of the patent at issue in this case; correct?

**A. I do understand that, yes.**

Q. Do you also understand that Bain Capital is a major investment -- investor behind Alkeus?

**A. I saw Bain Capital mentioned in some of the documents. I don't know the full portfolio of their investors.**

Q. So -- and that's all just to provide foundation. I'm not trying to get into your personal life, of course. But I'm just trying to understand if the investor behind essentially the patent owner in this case is also an investor in your company.

**A. Okay.**

Q. So I'll ask the question this way: Is Bain Capital currently an investor in any of your companies?

MR. FELDSTEIN: And I'll object that it's beyond the scope. And I'll tell you, doctor, he's allowed to ask whatever questions he wants. You are not obliged to give him your business confidential information.

THE WITNESS: Okay. So do I answer?

MR. FELDSTEIN: You need to respond to him.

THE WITNESS: Okay. The answer is they are not an investor in our company.

BY MR. MILLS:

Q. Sitting here today, you can't rule out that Bain Capital is one of the investors to which your company is reaching out for funding; is that correct?

**A. We will reach out over the course of the next few months to probably 100 firms.**

Q. And among those 100 firms, one of those is Bain Capital; is that correct?

**A. I don't know that we've made a decision on that or not.**

Q. Have you previously been involved with any company that's funded by Bain Capital?

**A. Can you repeat the question?**

Q. Have you previously been involved with

any company that is funded by Bain Capital?

**A. That's a hard question to answer because I don't know other companies that they have funded.**

Q. To the extent that you are aware.

**A. To the extent that I'm aware, the answer is no.**

Q. Other than Ferrx Bio, have you founded any other companies?

**A. Yes.**

Q. Can you tell me them?

**A. Yes. So in reverse chronological order, Seeing Medicines is the name of a company, kind of spelled the way it sounds like it should be spelled, Seeing and then the word Medicines, all one.**

**Prior to that, a company called Regenavision -- Regenasight, actually, I apologize, Regenasight, R-e-g-e-n-a-s-i-g-h-t. That's kind of the same company that was replaced by Advanced Ocular Technology, AOT.**

Q. Any others?

**A. Those are the only others that I'm aware of or that I recall.**

Q. Now, I'd like to ask you about your background. You are an ophthalmologist; is that

correct?

**A. Yes, that is correct.**

Q. As an ophthalmologist, you are a medical doctor?

**A. Yes, I am.**

Q. Who specializes in the eye; is that correct?

**A. Yes.**

Q. What's the difference between an ophthalmologist and --

**A. Optometrist?**

Q. -- optometrist?

**A. So ophthalmologists go to medical school prior to sub-specializing in ophthalmology. So if you start the clock at the time of college graduation, essentially in ophthalmology, an ophthalmologist would have four years of medical school after that, do a one-year internship, usually in general medicine and general surgery, and then do a three-year residency in ophthalmology, so now we're up to eight, and then do typically one to two years of fellowship after that.**

**So it's about eight to ten years of training after graduation from college. It**

**prepares people for the full scope of management of complex patients. Ophthalmologists do surgery around the eye, around the face, depending on the specialty of the ophthalmologist. We treat general medical patients very early on in our career, although that becomes less as we sub-specialize.**

**The optometric program historically sort of started with, it's a three-year training program, some of them are shortened to two years actually if you have a graduate degree, but essentially teaches you to do eye exams and detect abnormalities. It's nonsurgical. In most states optometrists were not licensed to prescribe medications for a long time and now there are states in which they can prescribe eyedrops and some other medications. One state, Kentucky I think, allows optometrists to do laser surgery and that's an exception, not the rule.**

Q. Approximately when did that transition occur?

**A. In Kentucky, about eight years ago, ten years ago.**

Q. You mentioned at the beginning of an ophthalmologist's career, they might treat the body more generally as they're beginning and then they

specialize?

What's the difference between an ophthalmologist and an internist?

**A. So, ophthalmologist training and internist training completely overlap for the first five years after college because we would all go to medical school for four years, and medical school doesn't have ophthalmology as a clinical elective. It might be like two weeks during medical school. And then we do a general medical internship, and that's taking care of hospitalized patients essentially with a variety of conditions, not related to their eye at all.**

**For an internist, they would then, after that first year of internship, they would then typically continue for two more years in that program, and then they'd be an internist, and they may sub-specialize as well into cardiology or gastroenterology or something similar to that. But at that point, after the one-year internship, ophthalmologists essentially go into separate training programs for eye diseases.**

Q. Are internists qualified to treat ocular disorders?

**A. Well, I think that internists do treat**

**simple things, you know, for example, a red eye in a patient, they might just put the patient on topical antibiotics rather than send them to an ophthalmologist, but by and large, most internists stay away from it.**

Q. If we are talking about something like macular degeneration, an internist isn't the right person to be treating macular degeneration in a patient; is that correct?

**A. I think that is correct, yes.**

Q. Now, you mentioned medical school, the internship, residency. Before that, an undergrad, is there a prerequisite degree that's required to become an ophthalmologist?

**A. So, an undergraduate, there are prerequisites to apply to medical school, and you can't submit an application without taking a series of courses in medical school that are related to either biology or chemistry or some combination thereof.**

Q. So you are not required to have a degree in biology or chemistry to go to medical school as long as you have sufficient prerequisite courses; is that correct?

**A. That is correct, yes.**

Q. In your particular case, instead of a degree in biology or chemistry, your degrees are in physics; is that correct?

**A. That's correct.**

Q. So you hold yourself out as an expert in ophthalmology; is that correct?

**A. Yes.**

Q. You are not an expert in the law; is that correct?

**A. I am not an expert in the law; that is correct.**

Q. Do you hold yourself out as an expert in medicinal chemistry?

**A. I would not classify myself as an expert in medicinal chemistry.**

Q. Do you hold yourself out as an expert in enzyme kinetics?

**A. I have some knowledge, but would not hold myself out as an expert.**

Q. You mentioned the RPE cells; do you remember that?

**A. Yes.**

Q. So tell me in a high level overview, what is the role of the RPE cells in the eye?

**A. So the RPE cells are the cells which**

separate the -- so in the back of the eye, there is a multilayered structure, so the innermost layer is the retina, r-e-t-i-n-a, and the RPE cells, the retinal pigment epithelial are immediately beneath the retina, and then beneath that is the blood supply to the outer portion of the eye which is something called the choroid or choriocapillaris. So the RPE cells sort of sit in between two important layers, the retina itself, and then on the other side of the RPE cells are the blood that's flowing which gives nutrition to the outer retina.

The pigment epithelium or RPE has multiple functions. And the normal functions include re-isomerizing vitamin A, so bringing it back, because otherwise in the absence of that function, what would happen is you'd only see light once. You know, you'd open your eyes at birth, the light would go on and then everything would go dark, because the pigment has to be turned back into a form that it can receive light again. So pigment epithelium is very heavily involved in that process.

It shuttles nutrients back and forth between the blood flow on one side of it and the

retina on the other side of it. It recycles waste products from the retina. So as an example, the photoreceptor cells that perceive vision, those are replaced at a certain rate. In most species, essentially about 3 percent of the cell is ingested by the pigment epithelium on a daily basis so it takes about one month to get completely new outer segments. It's almost like this constant pruning, if you will, of a tree in your backyard where you remove 3 percent, it grows a little more, you remove 3 percent again. The pigment epithelium does that with the photoreceptor outer segments.

It provides something called the blood-retinal barrier. So the blood vessels underneath it in the choroid are leaky. They are not tight blood vessels. A lot of blood vessels in our body are basically watertight and protein-tight, meaning that, think of your garden hose, they'll carry blood from one point to the other, but there won't be any leakage of material coming out of it.

The back of the eye, that's actually not true. The layer underneath the pigment epithelium is like a leaky garden hose, and the pigment epithelium actually has junctions between the

**cells. If I can use the tile analogy again for just a second, the grout in-between the tiles is the tight bond between the RPE cells to stop water from leaking out from underneath it. So it has multiple functions.**

Q. Is it a mistake that the body has these leaky vessels there? Is that something that just evolution forgot to fix, or is there a role for that?

**A. Well, that's a good question. I think there's a role for it. I think there is a role for it.**

Q. Do you have a sense as to what that role is?

**A. Well, I don't know what would happen if you actually just tighten those and did not allow material to leak, but material from the blood supply has to get into the pigment epithelium so that's probably why they leak to begin with, because a lot of metabolism happens there, but you don't want it to leak through the pigment epithelium and get water or exudates on the other side of the tile. You don't want that to happen.**

Q. Okay. So you talked about the RPE cells as kind of a gatekeeper, in fact, I think you

called it a blood-retinal barrier. Is that kind of like a blood-brain barrier?

**A. It's very similar. There are two places where there is a blood-retinal barrier in the back of the eye, the inner and the outer blood-retinal barrier. So the outer blood-retinal area, "outer" meaning it's closer to the outside part of the eye, is the one that I just described, where it's made up of the tight junctions between adjacent or nearby RPE cells, and then the inner blood-retinal barrier exists within the retinal blood vessels.**

**So unlike the choroid that has leaky blood vessels, the retina itself has a blood supply on the other side of it and that is formed by -- there, there are tight junctions in-between the cells that essentially stop the blood vessels from leaking.**

Q. So you mentioned the RPE is performing as a barrier and at the same time it's shuttling nutrients in the eye.

Can you tell me what nutrients the RPE cells function to shuttle into the eye from the rest of the blood supply in the body?

**A. It's ubiquitous. Anything that's in blood would come out of the choriocapillaris and**

**would get into the pigment epithelium. You know, glucose, sugar would do it. I mean, oxygen goes through that layer. Without that, the cells of the photoreceptors would die. There are lots of -- I mean, calcium, magnesium. There are a lot of things that go back and forth between them.**

Q. You mentioned nutrients. Are there vitamins that go through the RPE cells?

**A. So the RPE cells do have a role in vitamin. So vitamin C -- it's complex. Vitamin C is also present at very high levels in the vitreous on the other side. So I'd say vitamin C certainly -- there's something called re-isomerization, almost like reloading the spring on vitamin A itself on the visual chromophore, so there are vitamins that are involved, yes.**

Q. I want to make sure I understand.

So first you mentioned vitamin C and then you mentioned vitamin A. So is it correct that the way that the body supplies vitamin A to the retina is through this blood-retinal barrier formed by the RPE cells?

**A. So vitamin A in the circulation would be in the choroid or the choriocapillaris, which are the blood vessels underneath. That would get taken**

**up by the RPE cells and -- but most of the vitamin A that is coming into the RPE cells, that should come in from the other side from visual pigments of the photoreceptors.**

Q. Okay. So I think I understand what you are saying. So the RPE cells are kind of a wall. There is the retina on one side and there is the blood circulatory system of the body on the other side. And on the retinal side, you are getting the used-up vitamin A from the visual cycle, and then from the circulatory system side, you are getting brand new vitamin A coming into the RPE cells as well; is that correct?

**A. You'll get multiple nutrients including vitamin A from the other side.**

Q. So the circulatory system of the body is filling in for the vitamin A that you need in your eyes to the extent you don't already have them in there; is that correct?

**A. The circulatory system for the body has the ability to add more vitamin A to the system. The major role of the pigment epithelium in the visual cycle is actually to just take the chromophore, the light-sensing molecule that's coming from the photoreceptors, and then to**

**basically change its conformation. Conformation is sort of the way the molecule looks in three dimensions, so that it's ready to receive light again when it's brought back to the photoreceptors.**

Q. Okay. So I want to make sure I just understand the two functions. So one of the functions of the RPE is that it receives the used-up vitamin A and it changes its conformation to make it ready to receive light again; correct?

**A. That is correct. That's the major function.**

Q. And a second function of the RPE is that this is the pathway through which the body supplies vitamin A to the eyes in the first place?

**A. Vitamin A from the circulation will come into the pigment epithelium and then goes to the photoreceptors, yes.**

Q. What would happen if we just cut out the vitamin A from the eyes, if we turned off the RPE so that you didn't have any vitamin A in the retina?

**A. Well, so there would be -- long term, you wouldn't be able to see because you won't have any molecules or be able to perceive light because the chromophore, which basically means the**

**light-activated part of the molecule, what's absorbing the light, the chromophore has something called 11-cis-retinal, which comes from vitamin A, and that's the only part that actually detects light in photoreceptor cells. So if you don't have that, you are not going to see anything. You are not going to see anything.**

Q. So if you don't have any vitamin A, you are not going to see anything just because there is no 11-cis-retinal on there to see.

You said that's long term. How long does it take for that to happen?

**A. I don't know the answer to that.**

Q. So if we cut off vitamin A from the retina for six months, is that sufficient amount of time for you to no longer be able to see?

**A. I don't know the exact answer to that. I suspect that would be plenty of time to cause damage.**

Q. Okay. So after this six months of no vitamin A, then we bring the vitamin A back, does everything go back to normal?

**A. So I don't know the answer to that, but there would be danger that you'd have cell death and other secondary processes from that kind of**

**severe nutritional deprivation, but I don't know the answer to that.**

Q. Is it correct that long-term deprivation of vitamin A leads to receptor -- photoreceptor cell death in the eye?

**A. Yes, I think that is correct.**

Q. And is that something that was known to ophthalmologists before September of 2007?

**A. That long-term vitamin A deprivation would lead to cell death? There is an old literature on vitamin A and there are nutritional studies that were done prior to 2007, looking at the ocular side effects, but there are systemic side effects as well of vitamin A deprivation, and there are numerous changes that happen in the eye.**

Q. And my question is specifically about photoreceptor cell death. So before September 2007, did ophthalmologists know that if you deprived the retina of vitamin A long term that that leads to photoreceptor cell death?

**A. I think there was evidence that long-term vitamin A deprivation would lead to structural changes in the retina that might be irreversible, but I don't know how long that period of time is.**

Q. And the structural changes in the retina

that might be irreversible resulted in a loss of vision; is that correct?

**A. Once you develop structural changes in the retina, you would have vision dysfunction associated with it.**

Q. So right now we're talking about irreversible damage to the retina, irreversible loss of vision.

There is also some temporary vision problems that come from a loss or a reduction of vitamin A to the retina; is that correct?

**A. Depending on the time period you're talking about, I suspect that there is a short period of time during which you could deprive the tissue of vitamin A, but not have it be irreversible.**

Q. So in that short-term deprivation where the damage is not yet irreversible, you still have the adverse consequence of, for instance, night blindness; is that correct?

MR. FELDSTEIN: Object to the form.

**A. Can you either repeat that or clarify it a little bit?**

Q. Let me start by asking: What is night blindness?

**A. Night blindness is a term that's used to describe difficulty in patients functioning under low levels of visual light, so essentially patients have more trouble in dim light conditions than they do in bright light conditions.**

Q. Is it correct that night blindness is a symptom of macular degeneration?

**A. So night blindness is a symptom of certain retinal diseases. Night vision actually comes from the rod photoreceptors, not the cone photoreceptors. So this is different in different species. But when you look at humans, their highest density of cone photoreceptors is actually in the macula and their highest density of rod photoreceptors is actually in the periphery.**

**So for night blindness, the patient's symptoms are usually worse if they have a retinal disease that's outside of the center part, so instead of the macula, it's actually the extramacular tissue, if you will, often the rods.**

Q. What is delayed dark adaptation?

**A. So delayed dark adaptation basically means that there is an abnormality in a patient's ability to adjust from light conditions to dark conditions or dark conditions to light conditions.**

**So if someone without retinal disease walked into a cave, you know, out on the beach, there is a certain period of time that it would take you to get dark adapted, and that may be about 30 seconds before you start seeing some detail, 60 seconds, but most people experience this once you are in the cave for like 10 minutes. You are completely dark adapted and all of a sudden you start seeing things you weren't seeing when you first walked in.**

**There is also an effect going the other way, you know, from a dark cave to a light, that's usually a little bit quicker adaptation where you are sort of blinded by the brightness of the light and then your retina resets its sensitivities. You can function in those conditions.**

Q. These delayed adaptation deficiencies present a problem for people when they are driving at night; is that fair?

**A. Delayed dark adaptation will give you all sorts of symptoms. That would be one of them, yes.**

Q. And what other problems are known to exist as a result of delayed dark adaptation?

**A. I'm sorry, can you repeat that?**

Q. What other difficulties are known to

exist from delayed dark adaptation?

**A. I mean, I think patients sometimes have experienced where it's difficult to walk at night, let alone drive at night, yet they are walking through the woods, they are walking on a trail, and they have retinal disease that is just going to take them forever to adapt to those conditions, or they may adapt completely. Somebody without a retinal disease might take them five or ten minutes, but then they can function in a dark trail with a little bit of moonlight, where somebody who has severely impaired dark adaptation might not. It may take them too long or they may not recover to a level that they feel safe.**

Q. Is delayed dark adaptation ever associated with macular degeneration?

MR. FELDSTEIN: Object to the form.

**A. Can you repeat that?**

Q. Is delayed dark adaptation ever associated with macular degeneration?

MR. FELDSTEIN: Same objection.

THE WITNESS: Answer the question?

MR. FELDSTEIN: Yes.

I can answer. Delayed dark adaptation is associated with diseases that also

cause degeneration of the macula.

Q. Can you give me some examples?

**A. Stargardt's disease would be an example. So that would be a good example of it, I think, but essentially for an abnormality of delayed dark adaptation, you need to affect the peripheral retina and plus affect the macula would be classified as a macular degeneration.**

Q. I'd like to go back to the visual cycle. You were talking about 11-cis-retinal as being the conformation that's prepared to receive the light to allow vision; is that correct?

**A. 11-cis is, yes, is the configuration that absorbs light.**

Q. And when the light hits the 11-cis-retinal the conformation of the 11-cis-retinal changes; is that what you said?

**A. The conformation of 11-cis-retinal changes. It goes from a cis configuration to a trans configuration.**

Q. Okay. So that at that 11 position, it goes from cis to trans; is that right?

**A. The molecule changes shape so that there is no bend any further at the 11 position basically.**

Q. At that point, the molecule is called all-trans-retinal; correct?

**A. Yes.**

Q. Is it correct that all-trans-retinal is an essential molecule for vision in a human being?

**A. So the transition from 11-cis to all-trans has a variety of states called meta states in-between, so it actually -- so what actually happens is at the 11-cis, when it changes shape, it starts to affect the shape of the molecule that it's embedded in. It essentially starts changing rhodopsin, and then that change in rhodopsin then leads to downstream biochemistry which initiates the signal for vision.**

**In the all-trans portion, it's like you have a preloaded spring, and as the spring is unwinding, that's when the visual signal starts, and by the all-trans, the spring is completely unwound. It doesn't have any visual function anymore. It just needs to be released, you know, brought to the pigment epithelium and then reloaded into its light-absorbing shape.**

Q. So does the body ever just unwind the spring part of the way and not make all-trans-retinal?

**A. Not to my knowledge. It doesn't mean that an aberrant photon doesn't do that. I would say not to my knowledge.**

Q. So the way our bodies are designed to work is I have a coiled-up spring, which is 11-cis-retinal, and then when the spring is popped all the way and released so that I've been able to see, now what I'm left with is the all-trans-retinal; correct?

**A. The all-trans-retinal which is then released from rhodopsin, the molecule that it was in, and then gets transported to be recycled and brought back.**

Q. I want to take this step by step because I want to make sure I have it all correct.

**A. Yes.**

Q. So this step of conversion from 11-cis-retinal to all-trans-retinal takes place in the RPE cell; correct?

**A. So that actually takes place -- this is really confusing, so that actually takes place in the photoreceptors. So the photoreceptor cells are containing -- have rhodopsin in them and the light-absorbing portion of rhodopsin is the 11-cis form.**

Q. Okay. And photoreceptors, are those the rods and the cones you were talking about earlier?

**A. Yes.**

Q. There is also a term I saw called "outer segments of the photoreceptor cells." So tell us, please, what is the outer segment of the photoreceptor cells?

**A. So photoreceptors are an unusual cell in the body. So most cells in our body kind of look like round circles. Sometimes they look like an amoeba. They look like a fried egg with irregular borders around them. But photoreceptors have a unique configuration where they have a small round nucleus, which is the part that basically does all the normal cellular functions, but then they have a projection called a rod. The projection looks like a rod, which is where it got its name from. And that's the light sensitive part of the cell. That's where all the rhodopsin molecules are. 95 percent of the rhodopsin molecules are in the rod outer segment.**

**If you think about it, it's an official way to really capture light because you want -- so the light is moving in parallel to the rod. So if you have a glass rod, the light would have to**

**traverse that entire rod. And if it gets absorbed by any other rhodopsin molecules it encounters along the way, then that's a signal for vision.**

**So the rod photoreceptors are elongated. They are usually parallel to the direction of light so they can detect the light, and they've got rhodopsin molecules stacked, almost stacked vertically so that the probability of a photon or particle of light going through it and not being detected is actually quite low.**

Q. So the outer segment -- sorry, it's the outer segment?

**A. Outer segment yes.**

Q. The outer segment of the rod or the cone respectively is the portion of that photoreceptor cell that's exposed to the light; is that right?

**A. So the entire cell is actually exposed to light. The way that I think about it is the outer segment is the part that has been optimized to actually detect the light because of its shape and where the rhodopsin is.**

Q. When you are talking about the rhodopsin, each one of those rhodopsins has a molecule of vitamin A in it; is that correct?

**A. Each rhodopsin has an 11-cis-retinal in**

**it, yes.**

Q. And that 11-cis-retinal is a particular conformation of vitamin A; is that correct?

**A. The 11-cis-retinal has -- the main part of its structure overlaps with the structure of vitamin A, but it's different because the end is a little bit different and the way it's bound to the protein. It's not floating free. It's actually bound at one end, and that bond is actually what gets broken when the shape changes and the light -- so what happens is when light is absorbed, it changes the shape. The shape change leads to a shape change in the protein around it, in the rhodopsin around it, and also when it changes its shape the bond that's holding it in there actually gets cleaved, and then the 11-cis-retinal is now all-trans. The signaling for vision has already been done. The light has already been absorbed, and now it's going to go outside the cell and be released by rhodopsin, get transported to a different cell, to the RPE, and then kind of reload it as a tightly wound spring again.**

Q. All of this 11-cis-retinal is derived from vitamin A; is that correct?

**A. The 11-cis-retinal is derived from**

**vitamin A, yes.**

Q. So in the step where the 11-cis-retinal becomes all-trans-retinal -- just for convenience, can we call all-trans-retinal "ATR"?

**A. Yes.**

Q. And then so you mentioned that after the preloaded spring is completely spent, the ATR is still in the outer segment of the photoreceptor; correct?

**A. Can we go back to all-trans? But yes.**

Q. Yeah, we can do that if that's easier.

**A. Thank you.**

Q. And then you said that the all-trans-retinal is going to be transported from the outer segment of the photoreceptor ultimately to the RPE cell; correct?

**A. Yes.**

Q. So in the visual cycle, what is the next form that this all-trans-retinal becomes, the visual cycle?

**A. So it gets -- it has to leave one cell and enter another cell, which is not a simple mechanism, because you need a protein that's going to carry it across the cell membrane. Somebody has to get -- help it get across the moat, if you will.**

Q. I want to stop you there to make sure I understand. So to do the next step in the cycle, it can't stay in the outer segments, it has to go to the RPE; is that correct?

**A. It has to go to the RPE, correct.**

Q. Just as a threshold because I want to make sure we have the right terminology, what is the next form of the molecule, what's the name of it, that we're going to get to?

**A. It's going to go to the RPE in the same form, and then once it's in the RPE, it will get chemically modified, so all-trans-retinol with an o-l at the end, it's an alcohol.**

Q. Okay. So the first form in the visual cycle is 11-cis-retinal; correct?

**A. Correct.**

Q. The second form is all-trans-retinal; correct?

**A. Yes.**

Q. And then the third form is all-trans-retinol; correct?

**A. Yes.**

Q. And the difference between all-trans-retinal and all-trans-retinol is that instead of being an aldehyde, it's an alcohol; is

that correct?

**A. It's an alcohol with an o-h group at the end.**

Q. What is it that converts the all-trans-retinal to all-trans-retinol in the body?

**A. What's the chemical reaction that does it?**

Q. Just how does it happen?

**A. I mean, there is a series of enzymes at different places in this visual cycle that assists in it occurring. This transport, the molecule has to physically move from one place to the other and then there are specific steps in the visual cycle where other molecules, the enzymes, are essentially involved in doing the conversion.**

Q. So there is an enzyme that converts all-trans-retinal to all-trans-retinol in the RPE cells; correct?

**A. There is an enzyme in the RPE cells that assists with the conversion, yes.**

Q. And that enzyme does not exist in the outer segments of the photoreceptor cells?

**A. Well, it doesn't exist at all or it doesn't exist in sufficient quantities to do the job because the retinol is being -- that conversion**

**is happening in the pigment epithelium. I can't rule out that there is a few molecules in it, but essentially it has to be transported.**

Q. It's important for the all-trans-retinal to be transported from the photoreceptor outer segments to the RPE so that the enzyme in the RPE can convert the all-trans-retinal to all-trans-retinol; correct?

**A. Yes, as the first step.**

Q. What would happen if you inhibited the enzyme that converts all-trans-retinal to all-trans-retinol?

**A. I mean, there is a figure in one of the exhibits. Can I look at it?**

MR. FELDSTEIN: Yes, we have -- his binder has most of the exhibits.

**A. But generally speaking, if you interfere with this process, right -- first of all, there are diseases. You know, each of these enzymes, there are essentially diseases that occur because you've inhibited this step, and I'd have to refresh my memory and look at one of the actual exhibits to tell you which enzyme and which disease it is. But if you interfere at different steps, you get disease.**

Q. In general, like what are the symptoms of the disease that you get when you interfere with the visual cycle?

**A. Well, it depends on what the interference is. I mean, if you -- so a simple detachment of the retina, so patients develop retinal detachments, so now you've separated the photoreceptors from the pigment epithelium, and they don't see in that area because now there is space. There is a lot of space between the cells, so now what happens is you shine the light on the patient, you get better retinal attachment. They see light, but they are not making 11-cis anymore so then their vision basically goes dark. They just see once and then that's it until you fix the retinal detachment for them.**

**So you need the integrity of this visual pathway in order for vision to function properly. If you interfere at any step, you are going to cause the next molecule not to be reduced and then a backup of the previous molecule or you may get deposition of abnormal molecules. There is a variety of things that can happen, none of which are good.**

Q. So focusing on this step of converting

all-trans-retinal to all-trans-retinol, which occurs in the RPE cells, if that doesn't happen, then because you are never getting the all-trans-retinol, you are stopping the visual cycle; is that correct?

**A. You would be stopping the visual cycle if you interfere with that, correct.**

Q. And then a second consequence you mentioned is that you are going to create a backup of the predecessor molecule which in this case is all-trans-retinal; correct?

**A. If you stop that step -- well, unless the patient is totally in the dark, as soon as you shine any light in the system, the 11-cis will convert to all-trans and then it will stop.**

Q. So are there maladies associated with a backup of an increase in the predecessor molecule all-trans-retinal that isn't being converted to all-trans-retinol?

**A. There are diseases that occur because of that, yes.**

Q. Can you tell us what those are?

**A. What I'd like to do is look at the figure and sort of refresh my memory because it's interrupting different steps, so it will just take**

**me a moment.**

Q. When you find what you are looking for, just go ahead and tell out loud so that we are all looking at the same thing.

**A. Okay, that is fine. Okay. So what I'm looking for is a paper by Baehr, which of course I don't have the exhibit number, so it's going to take me a moment.**

**I'm looking for, it's just two pages, it's written by Wolfgang Baehr, and that looks like it.**

**(Exhibit 2120, previously marked.)**

BY MR. MILLS:

Q. I'm not sure if I found what you are looking for, but I think maybe it's Exhibit 2120.

**A. 2120. That is so much faster than me thumbing through this.**

**Yes. This is what I'm looking for, so I just need a moment to look at this for a second.**

**(Pause.)**

**A. Okay. Can you repeat the question?**

Q. I asked whether there are maladies associated with an increase in the predecessor molecule all-trans-retinal in the visual cycle when it's not being converted to all-trans-retinol. You

said there were, and I said, can you tell us what those are.

**A. Okay.**

**So referring to Figure 2 of this exhibit which is Exhibit 2120, so it shows a visual cycle, it then also shows the different enzymes. It doesn't show all of them that are involved in this. And from retinal to retinol, it's not showing it, but there is a dehydrogenase that does that, which is stated in the previous page, "All-trans-retinal is reduced to all-trans-retinol by NADPH-dependent all-trans-retinol dehydrogenase."**

**Then at the next step, the disease would be Leber congenital amaurosis, the conversion, if you don't have efficient conversion of all-trans to the retinyl ester.**

Q. Can you tell me the name of the disease again?

**A. So Leber congenital amaurosis is one of the diseases that occurs if you don't have efficient conversion of the all-trans-retinol inside the pigment epithelium cell.**

Q. What are the characteristics of that disease?

**A. Essentially this is a disease present at**

**birth. It usually leads to severe loss of vision in children in a very young age. Patients develop loss of central vision and then night blindness. Most of the patients have lost significant if not all vision in child -- during childhood.**

Q. That's as a result of inhibiting the visual cycle?

**A. As a result of inhibiting the visual cycle, yes.**

Q. What other consequences would be predictable from inhibiting the all-trans-retinal dehydrogenase enzyme that the body uses to convert all-trans-retinal to all-trans-retinol?

MR. FELDSTEIN: Objection to form. Misstates the testimony.

**A. I'm sorry, can you repeat that.**

MR. FELDSTEIN: That's just for the record, you can answer.

**A. Can you repeat the question.**

Q. What other consequences would be predictable from inhibiting the all-trans-retinal dehydrogenase enzyme that the body uses to convert all-trans-retinal to all-trans-retinol?

MR. FELDSTEIN: Same objections.

**A. So the major consequences would be you**

**would not get recycling of the visual pigment, so a patient wouldn't be able to see. The retinal detachment, for example, I mean, patients are completely blind with the retinal detachment because this process has been completely blocked because of the mechanical separation of the cells, so that's probably the purest example, where the all-trans-retinal gets formed in the photoreceptors but then never makes it to the pigment epithelium for recycling and patients are blind.**

Q. I notice that there is, in this Figure 2 of Exhibit 2120, there is also an enzyme identified called 11-cis-RDH; do you see that?

**A. I do see that on the figure, yes.**

Q. Does that stand for 11-cis-retinal -- sorry, actually, can you tell me what it stands for?

**A. I'd like to go back to the paper. It usually stands for dehydrogenase, but I would like to look back at the paper for a moment.**

**It's a -- let's see. Reading from the previous page, "11-cis-retinol would then be oxidized to 11-cis-retinal in a reaction catalyzed by NAD-minus and NAD-dependent 11-cis-retinol dehydrogenases, which are other short chain**

**dehydrogenase family members. One of these, 11-cis-RDH" -- which probably means either retinal or retinol dehydrogenase, should be the latter -- "has been thoroughly characterized and its mutant forms are associated with the human condition, fundus albipunctatus."**

**So basically, this is a retinol dehydrogenase and there is a mutation in that that's been found in people that causes a retinal degeneration called fundus albipunctatus.**

Q. Is that disease also associated with loss of vision?

**A. That disease is also associated with loss of vision, definitely.**

Q. You've agreed that one of the predictable effects of inhibiting the body's conversion of 11-cis-retinol to 11-cis-retinal is a loss in vision?

MR. FELDSTEIN: Object to form.

**A. So inhibiting the conversion of 11-cis-retinol to 11-cis-retinal, it would be tantamount to inhibiting a major step in this pathway. I am not aware of any bypass pathways that would sort of fix that, and that should lead to retinal degeneration.**

Q. So that would be a bad thing; correct?

**A. I think that would be a bad thing, yes.**

Q. And this is all -- this reference is from 2003; correct?

**A. This reference is an editorial written in 2003, yes.**

Q. So by September 2007, you agree that ophthalmologists knew that it would be a bad thing to inhibit 11-cis-RDH; correct?

**A. Do you mind repeating that?**

Q. By September 2007, you agree that ophthalmologists knew that it would be a bad thing to inhibit 11-cis-RDH; correct?

MR. FELDSTEIN: Object. Object to form.

**A. I'm not understanding the last part. You mean 11-cis-RDH?**

Q. Yes. Let me ask the question again just to make sure I'm saying it correctly. It's a new question.

By September 2007, you agree that ophthalmologists knew that it would be a bad thing to inhibit 11-cis-RDH; correct?

MR. FELDSTEIN: Object to the form.

**A. So I think there's a difference between**

**inhibit and completely block the function of. So in the mutants example with fundus albipunctatus, I would have to go back and review the literature on that, but usually mutations will severely disrupt the function of either a protein, especially enzymatic proteins, so I think if you did not have functional 11-cis-RDH, that that would be -- that would be a bad thing.**

**Inhibit, you know, to me, I mean, 1 percent could be inhibition. 2 percent could be inhibition. I don't know what the consequences of that would be. But having it not functioning, 11-cis-RDH would be a bad thing.**

Q. So let me ask I think a more narrow question: By September 2007, you agree that ophthalmologists knew that inhibiting 11-cis-RDH significantly would be a bad thing?

MR. FELDSTEIN: Object to the form.

**A. I think there would have been concern in 2007 that if you had lack of function of 11-cis-RDH that that could have negative downstream consequences.**

Q. And the same is true of the all-trans-retinol dehydrogenase that converts all-trans-retinal to all-trans-retinol; correct?

MR. FELDSTEIN: Object to form.

**A. I think that you need function of that dehydrogenase for proper functioning of the visual cycle.**

Q. And the same is true of the RPE 65 enzyme that is responsible for creating the 11-cis-retinal; correct?

MR. FELDSTEIN: Same objection.

**A. So I think that for RPE 65, it was recognized that there would be negative consequences from that enzyme not working properly, and in fact there was a form of Leber's congenital amaurosis that was targeted for gene therapy later on because of that reason.**

Q. Thank you. I have a question about, on the left-hand side of this Figure 2 in Exhibit 2120.

**A. Okay.**

Q. Where it has an arrow saying from bloodstream and it's pointing to all-trans-retinol; do you see that? Through the chylomicrons.

**A. Where it says from bloodstream RBP, chylomicrons, and all-trans-retinol?**

Q. Yes. Do you see that arrow?

**A. I do see that arrow, yes.**

Q. What does that arrow indicate in the diagram?

**A. That the transportation of what's to the upper left gets to the lower right in the form of chylomicrons.**

Q. And what is it that's being transported in that arrow in this figure?

**A. Well, they don't say. I think they are implying from looking at the legend on the figure. They don't say. From the legend of the figure, "Rhodopsin receives its supply of 11-cis-retinal from the RPE, and the isomerized chromophore, all-trans-retinal, is recycled along the pathway."**

**The sentence above that, "All-trans-retinol, in parentheses, vitamin A, is taken up by the RPE from the bloodstream, converted to retinyl ester by LRAT and then stored."**

Q. So in the visual cycle, all-trans-retinol is vitamin A; correct?

**A. All-trans-retinol is vitamin A.**

Q. And vitamin A enters the visual cycle from the bloodstream via the RBP and the chylomicrons; correct?

**A. That is what that figure is trying to transmit, yes.**

Q. You agree that vitamin A is essential to the visual cycle; correct?

**A. I think that vitamin A is essential to the visual cycle.**

Q. You agree that vitamin A is essential to the ability of human beings to see; correct?

**A. I think that vitamin A is essential to the proper functioning of the retina into the visual cycle and that that is essential to vision.**

Q. Do you take a multivitamin personally?

**A. Do I take a multivitamin? I do not.**

Q. Do you have any patients who take multivitamins?

MR. FELDSTEIN: Object to the form.

**A. I think the answer to that is yes.**

Q. What percentage of your patients would you say take a multivitamin?

**A. Between 30 and 50 percent maybe.**

Q. Do you discourage your patients from taking a multivitamin?

**A. No, I do not.**

Q. Can you give me some examples of the multivitamins that your patients take?

**A. They take a very wide range of multivitamins. They take over-the-counter**

**nutritional supplements. People do this in addition to their food supply.**

Q. Can you give me any examples of popular multivitamin supplements that your patients take?

**A. I wouldn't have a good way of knowing that.**

Q. Have you ever heard of the Centrum multivitamin?

**A. I've heard of it, yes.**

Q. What is the Centrum multivitamin?

**A. It's a mixture of multiple vitamins, but I don't know the concentrations of each one.**

Q. Is it a pretty common multivitamin for individuals to take?

MR. FELDSTEIN: Object to form.

**A. I don't know how common it is, but I have patients who take it.**

Q. And you agree that the Centrum multivitamin includes vitamin A; correct?

**A. I don't know if it does or not. I'd have to look at the label.**

**(Exhibit 1065, Centrum Adults label, marked for identification.)**

BY MR. MILLS:

Q. I'm handing you what has been marked as

Exhibit 1065.

MR. FELDSTEIN: I'd object to Exhibit 1065 including for authenticity and relevance.

Q. So you have Exhibit 1065 in front of you?

**A. I have Exhibit 1065 in front of me.**

Q. And what does it appear to you that Exhibit 1065 is?

MR. FELDSTEIN: Object to the form.

**A. It's a document that is showing the chemical composition of Centrum Adults.**

Q. That's a multivitamin; correct?

**A. It's a vitamin that has multiple components, yes.**

Q. One of the components of the Centrum multivitamin is vitamin A; correct?

MR. FELDSTEIN: Object to form.

**A. Vitamin A is listed as one of the ingredients, yes.**

Q. In the Centrum multivitamin, what's the composition amount of the vitamin A?

MR. FELDSTEIN: Object to form.

**A. Vitamin A is 1,050 micrograms.**

Q. How does that amount of the vitamin A relate to the recommended daily allowance of

vitamin A?

MR. FELDSTEIN: Object to form. Foundation.

**A. Daily requirements of vitamin A are about 900 micrograms in males and about 700 or 750 micrograms in females.**

Q. My question was about the recommended daily allowance, so --

**A. About the --**

Q. Recommended daily allowance, RDA.

**A. That's what I'm referring to, the recommended daily allowance of it is 900 micrograms in males and 750 in females.**

Q. Okay. So the amount of the vitamin A in the Centrum multivitamin is a little bit larger than the RDA; is that correct?

MR. FELDSTEIN: Object to form and foundation.

**A. It's a little bit more, but they are also saying that 29 percent is in the form of beta-carotene, so if you are actually looking at the amount of vitamin A ingested, it's lower than the 1,050 micrograms.**

Q. You mentioned the RDA for a typical adult. Does the RDA for vitamin A for a lactating

individual differ from that for a normal adult?

**A. I do not know the answer to that.**

Q. Would it surprise you to find out that the RDA for a lactating individual is twice the .9 micrograms for an adult male?

MR. FELDSTEIN: Object to form, foundation.

**A. I don't have -- I didn't review any literature on the vitamin A requirements for lactating individuals.**

Q. You don't have an opinion on that one way or the other?

**A. I'm sorry?**

Q. You don't have an opinion on that one way or the other?

MR. FELDSTEIN: Object to form.

**A. I didn't review any data on it.**

Q. You were talking about beta-carotene. What is beta-carotene?

**A. Beta-carotene is essentially -- it's a provitamin found in many foods. It actually is a colored pigment that gives brightly colored vegetables that color, you know, carrots, red peppers, that sort of thing, and it's part of our food supply.**

Q. You referred to beta-carotene as a provitamin. Is beta-carotene a provitamin A carotenoid?

**A. Beta-carotene is a provitamin for vitamin A, and the word "carotenoid" corresponds to that chemical class, and it is definitely a carotenoid.**

Q. So it is correct to refer to beta-carotene as a provitamin A carotenoid; correct?

**A. It is correct to refer to it as a provitamin for vitamin A, and it's also correct to call it carotenoid.**

Q. So if someone were to call beta-carotene a provitamin A carotenoid, you wouldn't disagree with them; correct?

**A. I'd have to see the context, but not based on those two words, no.**

Q. How much vitamin A is in a single molecule of beta-carotene?

**A. So beta-carotene is essentially two vitamin A molecules. In size. In size, I'd like to add.**

Q. So when we eat a carrot, our body ultimately breaks the beta-carotene apart into the two vitamin A's; is that correct?

MR. FELDSTEIN: Object to form.

**A. So our body -- when people ingest beta-carotene, there is beta-carotene circulating in our blood, and there is also some vitamin A that has been produced by cleavage in the beta-carotene molecule.**

Q. Does the body store vitamin A in the form of beta-carotene?

**A. Can you repeat that again?**

Q. Does the human body store vitamin A in the form of beta-carotene?

MR. FELDSTEIN: Object to form.

**A. So vitamin A is stored, you know, most of it is stored in the liver. But you can have -- and they showed this in the AREDS -- you can have high-circulating levels of beta-carotene by ingesting beta-carotene, and it's still in the beta-carotene form.**

Q. And you said "the AREDS"?

**A. Yes, the Age-Related Eye Disease Study. The abbreviation for it is A-R-E-D-S.**

Q. Okay.

**A. Because they gave beta-carotene as a supplement, and then they actually measured levels in the bloodstream, so they were able to show that**

**when patients were given an oral beta-carotene supplement that the beta-carotene in their blood was higher than it was at baseline, significantly higher, actually. So there is some circulating beta-carotene and there is some beta-carotene that will be converted to vitamin A.**

Q. What was the dose that was administered of beta-carotene in the AREDS study?

**A. The dose of beta-carotene in the AREDS study -- I'd like to go back to the AREDS. I believe it was 15 -- let me just go back to the AREDS so I don't make a mistake. I think that was Exhibit 8, 1008. No, it's not 8.**

Q. 1008 I think is the Ortho Pharma.

**A. No, it's a different one.**

**(Exhibit 1022, previously marked.)**

Q. So maybe it's 1022.

**A. Yeah.**

Q. Is that the right one?

**A. 1022 is what I was looking for. And the dose is correct from what I remembered, the dose of beta-carotene is 15 milligrams.**

Q. Okay. They gave them 15 milligrams of beta-carotene every day; is that correct?

**A. That is correct.**

Q. How long did they do that?

**A. The AREDS study was several years. Let me just review it and see what this paper refers to.**

**So, for example, this paper has 6.3 years as the average, with an attrition rate of patients of about 2.4 percent being lost to follow-up.**

Q. Okay. Was this a large study or is it a niche study?

MR. FELDSTEIN: Object to form.

**A. They enrolled 3,648 participants.**

Q. So on average for 6.3 years, the study population is receiving 15 milligrams of beta-carotene every day; correct?

MR. FELDSTEIN: Object to form.

**A. On average, they were given 15 milligrams of beta-carotene daily for 6.3 years.**

Q. So that's 15 times the recommended daily allowance of vitamin A; correct?

MR. FELDSTEIN: Object to the form.

**A. So the recommended daily allowance corresponds to vitamin A, not to beta-carotene. So that they are different. They are not the same thing.**

Q. So what's the correlation? Does that

mean it's higher than 15 or lower than 15?

MR. FELDSTEIN: Object to form.

**A. You can't really tell because you don't know what percentage of the beta-carotene is being converted at a certain period of time. And it's not 100 percent converted, even the AREDS show that. But it's 15 milligrams of beta-carotene, some of it will be cleaved and converted to vitamin A and some of it will be circulating beta-carotene.**

Q. Okay. So this 15 milligrams of beta-carotene they are receiving every day caused their beta-carotene concentrations in their serum to go up after an average of 6.3 years; is that correct?

MR. FELDSTEIN: Object to the form.

**A. That is my recollection as shown in the paper, yes.**

Q. Did their serum vitamin A concentrations go up significantly?

**A. I'd like to look at a table to refresh my memory before I answer that. So I'm looking at Table 9.**

**(Pause.)**

**A. Okay. Can you repeat the question for me.**

Q. After an average of 6.3 years receiving 15 milligrams of beta-carotene every day, the vitamin A serum concentrations of the study population did not increase significantly as compared to the control population; correct?

MR. FELDSTEIN: Object to form.

**A. So the AREDS data listed two time points on that dose of beta-carotene. They looked at one-year follow-up and five-year follow-up, and the vitamin A levels and beta-carotene levels at those periods of time are shown in Table 9.**

**So I'm looking at them now. So your question is on the vitamin A levels or the beta-carotene levels?**

Q. My question is about vitamin A, and I'll ask it again just so it's in front of you.

So five years after receiving 15 milligrams of beta-carotene every day, the vitamin A serum concentrations of this study population did not increase significantly as compared to the control population in the AREDS study; right?

MR. FELDSTEIN: Object to form.

**A. So after five years of beta-carotene, the serum, the serum levels of vitamin A did not change**

**in a significant fashion over that five-year period of time.**

Q. And the same is true after one year; correct?

**A. So the one-year period of time, the vitamin A levels in serum did not increase which is unlike the beta-carotene levels.**

Q. Do you know whether the participants in the AREDS study were permitted to take a multivitamin comprising vitamin A?

**A. I'd like to go back and review the entry criteria for the study.**

**All right. So as part of their enrollment criteria, the second paragraph, which is on the top of page 3 states the percentage of patients who were taking Centrum and their study. At baseline 8 percent were smokers and 67 percent chose to take Centrum. "Of those who elected to take Centrum, 30 percent had been taking multivitamins or a supplement containing a study ingredient for more than five years before study entry."**

Q. Is it correct that two-thirds of the study participants were taking the Centrum multivitamin supplement?

MR. FELDSTEIN: Object to form and foundation.

**A. 67 percent were taking Centrum.**

Q. And 67 percent is roughly two-thirds; correct?

**A. Agreed.**

Q. So you agree that two-thirds of the participants in the AREDS study were taking the Centrum multivitamin supplement; correct?

MR. FELDSTEIN: Object to form and foundation. Misstates the document.

**A. I'm referring to the same document, page 3, and it basically states that two-thirds or 67 percent chose to take Centrum.**

Q. And you don't dispute the Centrum multivitamin they took comprised vitamin A; correct?

MR. FELDSTEIN: Object to form and foundation.

**A. I don't know if it was identical to this formulation. This one is called Centrum Adults, and I just don't know if they are different or not.**

Q. Do you dispute that the Centrum they took had vitamin A?

MR. FELDSTEIN: Object to form and

foundation.

**A. I'm not trying to be difficult, but this just says they were taking Centrum, but I know with Centrum, there is Centrum Silver, there is Centrum Adults, you know, they are vitamins. So I'm just not 100 percent certain that the Centrum formulation they are referring to in here contains vitamin A. It probably does. And I don't know if they are contained in exactly the same dose. I just don't know if it's the same medication or not.**

Q. As you sit here today, are you aware of any Centrum multivitamin that does not contain vitamin A?

MR. FELDSTEIN: Object to form and foundation.

**A. I'm not familiar with all the Centrum preparations.**

Q. Please take a look at page 8 of Exhibit 1022.

**A. Exhibit 1023?**

Q. No, sorry, the one we are looking at, 1022.

**A. Okay. Page 8?**

Q. Yes.

**A. Okay.**

Q. You see the last full -- or I guess it's the first full sentence at the top of page 8. It starts saying "The effect."

**A. The paragraph that says "Potential Adverse Effects"?**

Q. Sorry. Do you have a page 8 at the top right corner of your document?

**A. I do.**

Q. And does the first full sentence of the top of that page say "The effect of Centrum"?

**A. It does say that, yes.**

Q. So it says, "The effect of Centrum, which contains RDA doses of the study medications, on serum levels of antioxidants and zinc in this population was negligible."

Do you see that?

**A. I do see that, yes.**

Q. So when it says Centrum contains RDA doses of the study medications, you agree that that implies that the Centrum that the participants took included Vitamin A at least in the form of beta-carotene; correct?

MR. FELDSTEIN: Object to the form. Foundation.

**A. Well, I mean, they are not being specific**

**what the exact doses are, but it may be in the paper somewhere exactly what patients are taking. They do make the general statement. It reads as it does, "The effect of Centrum, which contains RDA doses of the study medications, on serum levels of antioxidants and zinc in this population was negligible."**

**I can't tell if they are talking every one of the things, you know, including like the copper in their study, if they are talking about the copper, the zinc, the vitamin C, the vitamin E, if they are talking about everything. And also that's sort of a little bit of a vague chapter, because it says RDA doses, and I don't know if the Centrum formulation the patients are taking is exactly the recommended daily allowance for each one. I'm not trying to be difficult; I just don't know exactly what that dose is.**

Q. So focusing on the sentence, it says that the Centrum these patients took contains RDA doses of the study medications.

Do you agree that's what it says?

MR. FELDSTEIN: Object to form. Misstates the document.

**A. So I agree that's the first part of that**

**sentence, yes.**

Q. Okay. When they say "study medications" -- and you just listed a bunch of them and I want to make sure we have a complete list -- so the study medications, it was a combination of beta-carotene, vitamin E, vitamin C, and zinc; is that correct?

**A. Well, yes, but they also included two milligrams of copper, which they should have. None of these studies really take that -- so copper is actually in the study medication, but then I don't know if they are referring to it or not in that sentence.**

Q. So I just want to make sure we are clear about the answer, so I'll ask -- but I'm going to put the copper in there so I don't want us to have a dispute about the copper.

**A. Okay.**

Q. So when they are referring to the Centrum containing RDA doses of the study medications, that refers to beta-carotene, vitamin C, vitamin E, zinc and potentially copper; correct?

MR. FELDSTEIN: Object to form and foundation.

**A. They are just referring to the study**

**medications. I think there is some vagueness in the sentence, if you want my honest opinion. And if I was writing it, I would have been much more specific.**

Q. So when we're talking about the antioxidants in the study medication, that refers to beta-carotene, vitamin C and vitamin E; correct?

MR. FELDSTEIN: Object to form and foundation.

**A. Those are antioxidants, yes.**

Q. Those are the antioxidants in the study medication in the AREDS study; correct?

**A. Those are the antioxidants in the study medication that was administered to patients in the AREDS, correct.**

Q. In the sentence before this and this sentence, they are looking at whether there is a change in, among other things, vitamin A from baseline to the treatment assignment or to the various treatments; correct?

**A. Let me read the sentence before. In fact, let me just take a moment to read the paragraph for a second.**

**(Pause.)**

**A. Actually, I'd like to take a break for**

**just a second, the amount of coffee I ingested this morning.**

Q. I should have mentioned before we started, we just can't take a break during a question.

**A. Okay.**

Q. So my question is just about this sentence.

So in this paragraph, they are talking about that there isn't a difference in vitamin A serum levels from baseline through the end of treatment; correct?

MR. FELDSTEIN: Object to form and foundation.

**A. So the sentence reads, "Vitamin A, beta-cryptoxanthin, and lycopene showed no statistically significant differences in change from baseline by treatment assignment." That's what the sentence reads, yes.**

MR. FELDSTEIN: Okay, why don't we take a break now.

MR. MILLS: We can go off the record.

(Recess taken from 10:45 a.m. to 10:52 a.m.)

BY MR. MILLS:

Q. Staying on that page 7, Exhibit 1022, there is three headings in bold that say Serum Levels, Changes in Serum Levels of Antioxidants and Zinc and Changes in Other Serum Levels.

Do you see those headings?

**A. I do see those headings, yes.**

Q. I want to ask you just to take a moment to read to yourself the paragraph under each of those three headings?

**A. All three of them?**

Q. Yes.

(Pause.)

**A. Okay.**

Q. So this section on serum levels is discussing the data in Table 9 that you took me to earlier; is that correct?

**A. I think this is referring to the data that's shown on Table 9, correct.**

Q. And here under the second heading, they report the serum level changes for each of vitamin C, vitamin E and beta-carotene; correct?

**A. Yes.**

Q. And then under the third heading, they say changes in other serum levels; correct?

**A. Yes.**

Q. And so under this third heading, they are talking about the vitamin A serum levels had no statistically significant difference in Table 9; is that correct?

MR. FELDSTEIN: Object to form.

**A. The last sentence says, vitamin A showed no statistically significant differences in change from baseline by treatment assignment.**

Q. And this whole paragraph is talking about the changes in serum levels; correct?

**A. Yes.**

Q. So that sentence when it's talking about vitamin A having no statistically significant difference is referring to that there is no difference in the serum levels of vitamin A; correct?

MR. FELDSTEIN: Object to form and foundation.

**A. Yes, I think that is what they are referring to.**

Q. Then they say that the RDA doses of the study medications in the Centrum multivitamin had at most a negligible effect on the serum levels in the study population; correct?

MR. FELDSTEIN: Object to form,

misstates the document.

**A. They do state that the effects of Centrum, which contains RDA doses of the study medications, on serum levels of antioxidants and zinc in this population are negligible.**

Q. Thank you. I want to go back to something that you we talked about earlier. We were talking about how do we get vitamin A in our bodies.

First, we talked about how does vitamin A get into our eyes, and then you mentioned how we get vitamin A in our bodies in the first place. You were talking about that it exists naturally in certain foods like carrots; right?

MR. FELDSTEIN: Object to the form. Misstates testimony.

**A. Beta-carotene exists in foods such as carrots.**

Q. So we eat the carrots with the beta-carotene and then our body breaks the beta-carotene apart so that we have the vitamin A; correct?

MR. FELDSTEIN: Object to form.

**A. From fruits and vegetables and, you know, carrots is probably the best example, we ingest the**

**beta-carotene, beta-carotene goes into our body and some of that is broken down into two vitamin A molecules per beta-carotene.**

Q. And then those vitamin A molecules can allow us to see by participating in the visual cycle; correct?

**A. Vitamin A is a crucial portion of the visual cycle, yes.**

Q. In addition to foods that naturally contain vitamin A equivalents, like beta-carotene, some foods are fortified with vitamin A; correct?

MR. FELDSTEIN: Object to form.

**A. I don't know the answer to that, as to whether vitamin A is added as a fortification to certain foods or not. It would not surprise me, but I don't have any first-hand examples of that.**

Q. So food fortification of vitamin A is not something that you evaluated for your opinions in this case; right?

**A. I did not look at food forti -- correct, I did not look at that.**

Q. Back to the AREDS study, these patients that for years were receiving 15 milligrams of beta-carotene and also taking a Centrum multivitamin, tell me about the study population;

what kind of individuals were these?

MR. FELDSTEIN: Object to form and foundation.

**A. I'd like to refer back to the document on the entry criteria.**

**(Pause.)**

**A. Okay. Can you repeat the question for me.**

Q. What were the characteristics of the patients that were enrolled in the AREDS study to receive 15 milligrams of beta-carotene and two-thirds of which also were taking a Centrum multivitamin for five years or more?

MR. FELDSTEIN: Object to form and foundation.

**A. So the patients who were enrolled, the enrollment criteria are stated in the study, but essentially they had evidence of age-related macular degeneration, which is a diagnosis made by an ophthalmologist on the basis of the retinal picture. And the eligibility criteria from the retina point of view were the presence of drusen, d-r-u-s-e-n, and they could be small, intermediate or large drusen, so all sizes were enrolled. And if they had geographic atrophy, it had to be not in**

**the center and also some pigment disturbance or pigment abnormalities in at least one eye or advanced macular degeneration or vision loss due to macular degeneration in the other eye. So that was roughly the enrollment criteria. And then they specify a little bit more about who they actually enrolled a little bit later on in the publication.**

Q. There were 3,640 participants enrolled in the AREDS study; correct?

**A. There were 3,640 people enrolled between ages 55 and 80, yes.**

Q. All of those participants had been diagnosed with age-related macular degeneration; correct?

MR. FELDSTEIN: Object to form and foundation.

**A. Part of the enrollment criteria, it typically is from macular degeneration, yes.**

Q. So you agree that the 3,640 participants enrolled in the AREDS study had been diagnosed as being patients in need of treatment for macular degeneration; correct?

**A. I don't agree that they needed treatment for macular degeneration, but I do agree that they had macular degeneration as an enrollment criteria.**

Q. And you agree that the 3,640 patients who were enrolled in the AREDS study had been diagnosed as patients having age-related macular degeneration; correct?

**A. I do agree that the patients enrolled were diagnosed with age-related macular degeneration, yes.**

Q. You agree that the AREDS study found that the combination treatment of zinc, 15 milligrams beta-carotene, vitamin C and vitamin E significantly reduced the odds of developing advanced age-related macular degeneration in the high-risk AMD patients in the study?

**A. I do agree that the nutritional supplement that also contained copper by the way reduced the risk of developing advanced macular degeneration in the second eye.**

Q. And this higher risk group of patients, tell me about those patients.

**A. So in general, these are patients who have already lost vision in one eye from macular degeneration, typically from the wet or the exudative form of the disease. So the reason that studies in general tend to focus on those patients is because those are the people that have the**

**highest rate of progression. It just makes sense because one eye has already progressed, so if you going to pick a study population that you think is going to have a bad natural history during your study, this would be the population to study.**

Q. So these patients in whom the AREDS study showed a statistically significant reduction in risk, you agree that they were all patients in need of treatment for age-related macular degeneration; correct?

MR. FELDSTEIN: Object to the form. Misstates his testimony.

**A. So I think that they were all high-risk patients. And it would be good to have a treatment that reduces the risk of them converting. You know, the word "all" is hard because you could have a patient who is 102 years old that would actually be outside the confines of the study. They really went up to 80, but they could have other multiple medical problems that may make you think their life expectancy is very short, so whether or not you treat someone under those conditions, it is a little bit less clear I think.**

Q. So in the context of age-related macular degeneration, whether someone is a patient in need

of treatment for AMD depends on how long they have left to live?

MR. FELDSTEIN: Objection to form.

**A. I think the way that I would phrase it is that you want to maintain quality of life during a person's lifetime, and you want to maintain their visual acuity during their lifetime. So ideally you'd want a treatment that does that for patients. You always need to temper what the treatment is, how interventional it is, what the side effects are, and what the person's general health might be.**

Q. It sounds to me that you are describing criteria for deciding whether to actually engage in administering a treatment; is that fair?

**A. Yes. I think I'm describing criteria that gets me away from the word "all" a little bit.**

Q. Okay. So whether it's all or whether it's just the group, the majority of the group, okay, the high-risk group who in the AREDS study were shown to have a reduced risk of developing advanced AMD when they were treated with 15 milligrams of beta-carotene, in combination with the other study ingredients, you agree that the majority of that group were patients in need of a treatment for AMD; correct?

**A. I agree that the majority of that group, it would be good to have a treatment that reduces their risk, yes.**

Q. So you seem to be reluctant to say that those patients were in need of treatment. Are you reluctant to say that the majority of those patients were in need of a treatment for AMD?

**A. I think I'm comfortable -- I am comfortable saying the majority need to be treated but there are caveats. You know, there are caveats with the treatment. So we'll probably get into this, but for example, beta-carotene increases the risk of lung cancer, so there are caveats that would cause you to be a little cautious.**

Q. So understanding that there are exceptions perhaps, but we are talking about this group of the higher-risk group in the AREDS study that were shown to have significantly reduced odds of developing advanced AMD, you agree that the bulk, the majority of that group were patients in need of treatment for AMD; correct?

**A. The majority of that group needs treatment to prevent the development of AMD in the second eye. There is one more caveat. I apologize, I tend to be very cautious in my choice**

**of words. The other caveat is that we always look for signs that patients are about to develop exudative disease, wet macular degeneration. So there are risk factors that we might see in the office that may make us think, you know, this person is going to develop blindness in the other eye in a short period of time. And also the opposite is true, where the finding is the other eye may be very benign. There is a lot of asymmetry that would make us a little bit less concerned about loss of vision during the person's lifetime.**

**I'm trying to say that many patients would need treatment, but recognizing that there are some that you might not treat for a variety of reasons.**

Q. So I understand that the treatment decision might be a separate decision. When we are just focusing on the question of, are they in need of a treatment, would they benefit from a treatment, the majority of the higher risk group in the AREDS study were patients in need of a treatment; you agree?

MR. FELDSTEIN: Object to form. Foundation.

**A. I would say the majority would need treatment. Majority I think means 51 percent. I feel comfortable.**

Q. And the majority are in need of a treatment for age-related macular degeneration; correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. Yes.**

Q. You even testified, haven't you, that based on this AREDS study, which was published in 2001, based on that, it became common to recommend the AREDS combination treatment for those high-risk AMD patients; correct?

**A. When the AREDS -- there were pre-publications, so for example, there were lectures at scientific meetings that predated this a little bit. But at around this time, patients coming in with high-risk macular degeneration that had already lost vision in one eye, this was used. This was used.**

Q. Did you ever -- did any of your patients ever use it?

**A. Did I ever give any of my patients the AREDS supplement?**

Q. Yes.

**A. Yes.**

Q. And that was common to do; correct?

MR. FELDSTEIN: Object to form.

**A. I would give my patients the AREDS supplement, yes. Recommend them.**

Q. What was the risk reduction, the decrease in progression risk for this high-risk population of AMD patients shown in the AREDS study?

**A. The reduction of risk in the second eye was about a 30 percent reduction risk.**

Q. And was that considered to be meaningful risk reduction at the time?

**A. Well, it was better than the alternatives we had, I'll say that much.**

Q. You agree that the results of this AREDS study were widely distributed; correct?

MR. FELDSTEIN: Object to form and foundation.

**A. "Widely distributed," you mean published and talks at meetings, that sort of thing? Yes. That was done.**

Q. I want to talk about serious adverse events. What does the AREDS study tell us about whether there were serious adverse events reported

in the study?

**A. I'd like to just refresh my memory on that section of it for a moment.**

Q. And if it's helpful for you, and you can look of course wherever you want to, but the top of page 2.

**A. The top of which page?**

Q. Page 2.

**A. Page 2. And they state that none were associated, but let me review this a little more.**

**(Pause.)**

**A. So on the top of page 2 of that same paper that we're referring to, the sentence reads -- this is part of their abstract by the way -- no statistically significant serious adverse events were associated with any of the formulations.**

**If you look at Safety Outcomes, which is page 8, there are some differences noted, but possibly they didn't rise to the level of serious adverse events, but there are some things with -- that were statistically significant between the treatment groups.**

Q. Going back to the abstract, under the Conclusion -- sorry, back in the abstract, so the

conclusion regarding adverse events in the abstract was that there was no statistically significant serious adverse effect associated with any of the formulations; correct?

**A. That is what the sentence says, yes.**

Q. Okay. Now, I want to ask about kind of the study design in general. This is a randomized study; correct?

**A. They describe it as an 11 center double masked clinical trial which usually implies that it is randomized.**

Q. It may be just even in the title.

**A. I mean, I can't imagine they wouldn't have randomized. My recollection of the study is it was randomized, and the title does use the word "randomized."**

Q. And it's a placebo-controlled study, correct?

**A. Yes.**

Q. What's the difference between a randomized placebo-controlled study and an observational study?

**A. Well, there is a few ways of using those terms. You could have a randomized clinical trial where the control population is randomized to**

**nothing, okay. And that's not as good of a design as a placebo-controlled study or the randomized was the placebo.**

Q. So the AREDS study was a large randomized placebo-controlled study; is that correct?

**A. Yes, it was.**

Q. Are you familiar with the journal in which it was published?

**A. Let's see where this one was published. Archives. Yes, I am.**

Q. Is that a reputable journal?

**A. Yes.**

Q. Was this a peer-reviewed article?

MR. FELDSTEIN: Object to form and foundation.

**A. So when it was published in 2001, this would have been a peer-reviewed article in the Archives of Ophthalmology.**

Q. What does it mean for an article to be peer-reviewed?

**A. Essentially when the article is submitted to a journal, the first person who looks at it is an editor, not usually the editor in chief, but a person reporting to the editor in chief, usually a scientist, who will then ask individual reviewers**

**to review the article, get the feedback from those reviews, typically two or three reviews, and then make a decision as to whether the article should be accepted as is, accepted with minor modifications, accepted with major modifications or just out-and-out rejected.**

Q. Is it fair to say that peer review is a quality control mechanism for publications?

MR. FELDSTEIN: Object to the form.

**A. Yes, yes.**

Q. In the scientific community, is a peer-reviewed article in a reputable journal like the Archives of Ophthalmology viewed as a more reliable indicator than, for instance, if there was a publication that was not peer-reviewed?

MR. FELDSTEIN: Object to form. Incomplete hypothetical.

**A. Yes. It does imply that because it's gone through that extra level of scrutiny.**

Q. Now, I want to talk about what you described in your declaration as a subsequent debate regarding AREDS study results; okay?

**A. Okay.**

Q. So my first question is about, you mentioned an AREDS 2 formulation; do you know what

I mean?

**A. I do know what you mean, yes.**

Q. Now, you lived through this time period. Can you confirm for me that the results of that AREDS 2 study were not published before September 2007?

MR. FELDSTEIN: Object to form and foundation.

**A. I do not recall the publication date of the AREDS, A-R-E-D-S, all capitals, 2.**

Q. When you wrote your declaration, did you think that the AREDS 2 study had been published before September 2007?

**A. I'd have to go back and refresh my memory as to the date of it.**

Q. Sitting here right now, you don't recall thinking that at the time you wrote your declaration; is that fair?

MR. FELDSTEIN: Object to form.

**A. I don't recall the date of the study, correct.**

Q. So you had some discussion in your declaration about some references that are discussing whether or not to apply the AREDS combination to populations other than the one that

AREDS found an improvement in their risk profile; correct?

**A. Yes.**

Q. So you said that it was common for the population, the AMD population identified in AREDS, it was common for ophthalmologists like yourself to follow the recommendation. These other references are saying, well, should we extend it to people that don't have -- are not high risk AMD, don't have these advanced higher risks.

MR. FELDSTEIN: Object to form.

Q. Is that fair?

MR. FELDSTEIN: Object to form.

**A. So there was an issue about how to apply the results of the AREDS. I think that there were several concerns. I think one of them was to -- was directed at exactly what you're getting at. You've got these high-risk individuals, okay. The study has just shown this benefit. Do you want to extend the results to lower-risk individuals? So I do think that that was an important controversy that was going on at the time.**

**There were others as well about applying the AREDS. And the other ones that came up, for example, was whether you should apply it to**

**everybody in that study population. So they themselves raised the issue of smokers, you know, in the AREDS study who had, I think there were roughly 30 percent higher risk of lung cancer if they were actively smoking.**

**But then very shortly thereafter, there were studies that looked at individual components, not necessarily for the eye, but for example, high levels of zinc became associated with Alzheimer's disease. The dose of vitamin E that was used, 400 international units, was subsequently associated with a higher risk of cardiovascular disease and stroke in women.**

**So AREDS comes out, results come out within a short period of time. Other studies are showing detrimental things, and you can't give people this oral supplement and have it go to their eye and not go to their heart or their brain or their lungs. So there were a variety of issues that were really brought up shortly afterwards.**

Q. I want to start with that first concern, which is applying it to a different group of AMD patients.

**A. Yes.**

Q. So in your declaration, you used the

phrase "primary prevention of early AMD." The controversy was that there was a common perception, it had long been suggested that vitamin A or beta-carotene might be useful for the primary prevention of early AMD. So when it talks about primary prevention of early AMD, is that different from the AREDS study where they are talking about the high-risk patients whose risks were reduced using the AREDS combination?

MR. FELDSTEIN: Object to form.

**A. I'll answer that. I want to look at the paragraph that I wrote related to this in my declaration before I answer that. But I'm happy to answer that.**

**What paragraph are you on? I can find it by thumbing through but...**

Q. So I'm looking at page 46, the top of the page, and it bridges over. You are citing the Chong 2007, reference Exhibit 2144, and it's talking about ingredients that have little or no effect in the primary prevention of early AMD.

**A. Okay.**

Q. So my question is about that terminology, "primary prevention of early AMD." Is that a different population of patients than the high-risk

AMD patients for which it had become common to recommend the AREDS formulation?

**A. Okay. Let me just reread that section for a moment.**

MR. FELDSTEIN: I'm going to object to form.

**A. So that's a quote that's obtained from Chong, which is Exhibit 2144.**

Q. So in Exhibit 2144, do you see on the right hand-column of the first page there is a paragraph --

**A. Yes, I'm there.**

**(Exhibit 2144, previously marked.)**

Q. So the paragraph you are on, is it the one that starts by saying, "Dietary antioxidants have long been suggested as useful for preventing the development and progression of AMD"?

**A. Yes. I just want to take a moment to read a few lines before and after that.**

**Okay, so I've read both. Do you mind repeating your question for me.**

Q. Yes. So we are just looking at the Chong reference in that paragraph, so where it's talking about it had long been suggested as useful for preventing and it says the development and

progression of AMD; do you see that?

**A. First sentence?**

Q. Yes.

**A. I do see that sentence, yes.**

Q. Okay. So there is two things that they are talking about. There is a suggestion for preventing development of AMD, and there is a suggestion of preventing progression of AMD; right?

MR. FELDSTEIN: Objection. Object to form.

**A. They mention both of those in the first sentence, yes.**

Q. And are those two different things?

**A. Yes, I do think that they are two different things.**

Q. So they are saying there's two different types of AMD treatment that they are talking about, one would be a treatment for preventing development of AMD and another would be treatment for preventing the progression of AMD; correct?

MR. FELDSTEIN: Object to form, foundation.

**A. I think what they are saying is that the antioxidants, I don't want to just reread it, but the antioxidants have been suggested as useful. It**

**may turn out that if you have a particular drug that that actually might be useful both for development and progression, both. It might only be useful for the development, you know, sort of preventative, but then not be useful when the disease has actually started affecting patients, or the latter, it could not be helpful in preventing the disease from developing but could be very helpful later on. So you don't know. There is really three possibilities for how it could turn out, and they are carefully separated in my view.**

Q. So perhaps there could be a ven diagram, so there is two circles.

**A. Yeah.**

Q. And they are overlapping, is what you are saying, or potentially overlapping; right?

MR. FELDSTEIN: Object to form.

**A. I think what I'm saying -- I'd like to be clear about what I'm saying -- if you have a compound that you think is useful for macular degeneration, that that compound, if it turns out to be effective at all, could be effective for preventing development; it could be effective only for preventing prevention or it could be effective for both. There is three possible outcomes.**

Q. Okay. So there are some patients that already have AMD; right?

**A. Correct.**

Q. So those patients are in need of treatment for the progression of the AMD; correct?

**A. Well, so those patients are in need of treatment for progression of AMD, especially in their second eye if they've already had it develop in one eye.**

Q. And there is also a category of patients that maybe are in need of treatment to prevent the development or the onset of AMD; is that correct?

MR. FELDSTEIN: Object to form.

**A. So there are patients who need an intervention that would stop the disease from developing to begin with.**

Q. Okay. So the very last sentence of the paragraph there, when it's talking about something that's effective for the primary prevention of early AMD in people without signs of this condition, that's an example of people who are in need of treatment for preventing the development of AMD; correct?

MR. FELDSTEIN: Object to form and foundation.

**A. They are referring to a population of patients who you might think are at risk, but don't have signs of the disease yet, and they are just talking about whether or not antioxidant supplements could be effective in that patient population before they actually have any disease.**

Q. So that these people that don't have any disease that you are trying to prevent, you are trying to have primary prevention of early AMD in these people, are those people in need of treatment for AMD?

MR. FELDSTEIN: Object to form.

**A. You know, it's really an excellent question. You are getting into a very basic question, I think, in ophthalmology. So you don't want to treat people who are never going to have disease during their lifetime, right? I mean, you don't want to put tons of patients, some of whom nothing is going to happen if you do nothing, so you are not helping those patients by putting them on something to prevent a disease that is not going to develop during their lifetime.**

**So if you are going to prevent the development of AMD, you still want to have some high-risk characteristics, because even in**

**high-risk populations, 30 percent of patients develop macular degeneration. So for example, over the age of 65, in the United States, this is -- you know, it could be as high as 30 percent. But that means that 70 percent never develop the disease. So what you want is some way of identifying the high-risk individuals who benefit from treatment from the ones who really are in the low-risk category and are just never going to have anything develop. Sometimes it's simple like family history or something like that that would do it.**

Q. So if we had like a risk calculator, we can just put things in and it would tell us, because of your characteristics, you know, you are 51 percent likely to get AMD, that would be how we could determine if that's a patient in need of treatment in the sense of in need of primary prevention of early AMD?

MR. FELDSTEIN: Object to form.

**A. So an accurate risk calculator would be very helpful.**

Q. And does that exist today?

**A. So it's a good question. There are risk calculators out there. In fact, I had a patient walk in with something she had downloaded from the**

**internet, you know, almost in tears because it said her risk for developing macular degeneration was going to be over 50 percent. This is someone with a normal retinal exam. I had no idea where this data even came from; it didn't make any sense to me at all. But the presence of a calculator would be helpful.**

**I think some websites, including 23andMe, try and do this based on genetics, but I don't think there is -- I'm not aware of any long-term studies that show how accurate they really are.**

Q. So if somebody is buying Centrum at Costco and they are buying it because they think vitamin A is going to help keep them from getting macular degeneration, you can't say today as an ophthalmologist with reasonable certainty that that person is or is not in need of treatment for AMD if they haven't been diagnosed with any kind of retinal disorder?

MR. FELDSTEIN: Object to form. Incomplete hypothetical.

**A. I think what I try and tell patients is to go with the data that we have, okay. And the data that we have is they have to have really high-risk characteristics, not I might develop**

**macular degeneration one of these days, to be put on nutritional supplements and to have me recommend them.**

**Now, these are not prescription items, they are over the counter, and patients make these decisions by themselves and just go ahead and buy it, maybe because their sister developed macular degeneration, which is maybe a good reason; their neighbor developed macular degeneration, which as far as I'm concerned there is no evidence that it's transmitted, you know, like COVID, from one person to another. That makes no sense at all.**

**But the data actually shows that if you have high-risk characteristics, those are the patients who benefit the most from the sort of supplementation that was done in the AREDS, with caveats, with caveats.**

Q. When you say the high-risk characteristics, can you tell us what those are?

**A. So I think from the AREDS study, the high-risk characteristics were really advanced macular degeneration in one eye. It was actually applicable to a very small percentage of the patients. I think the AREDS did show that it lowered your risk in the other eye, and I would say**

**that I do recommend AREDS supplements for those individuals.**

**For patients who have very low-risk characteristics in the AREDS, the natural history of disease has to be poor in order for you to be able to tell if your treatment is doing anything. So the problem with intervening with patients with early macular degeneration is that their natural history is actually pretty good. You know, even if you have a few drusen, these little yellow spots in the back of the eye, in your 60s or 70s, even if you have a little bit of pigmentary change, the chances that you would lose vision if you do nothing are not that high, so you can't really design a study effectively unless you are looking at tens of thousands of patients to tell if your drug is going to work or not.**

Q. So for those patients that you were referring to just now that have a little bit of drusen in the back of their eye or a little bit of pigment change, those are patients that you, based on your expertise, would say are not patients that are in need of treatment for macular degeneration; correct?

**A. Well, the way that I would word it, I**

**choose to word it, is that if I had a treatment that was effective at lowering their risk from 5 percent to 1 percent and the side effects were almost zero, I probably would recommend it. Why live with a 5 percent risk when I can give you a 1 percent or a half of 1 percent or something? But the data is not there to bear that out. The data is not there, in my view, to back that up scientifically. We don't have that product.**

Q. Focusing again back on this Exhibit 2144, in that same paragraph, so we talked about the preventing the primary -- or the primary prevention of early AMD, so that's essentially prophylaxis; is that correct?

MR. FELDSTEIN: Object to form, foundation.

**A. It's prophylaxis against the advanced form. Now I will put in a caveat that patients with early AMD sometimes have symptoms. They are not blind. They haven't developed bleeding in one eye. It's not that level of symptoms. But patients sometimes can have a little bit of trouble driving at night or a little bit of trouble with reading with early macular degeneration. So those patients can have what I would call mild symptoms,**

**not mild because it's not important to the person, but mild compared to the other diseases we deal with.**

Q. So in this Chong reference, Exhibit 2144, it says that study did not specifically examine whether its supplements were effective for primary prevention of early AMD in people without signs of this condition.

Do you see that?

MR. FELDSTEIN: Objection, misstates the document. Form.

**A. So I do see the sentence that begins with "That study" and ends with "signs of this condition," yes.**

Q. Can you read that sentence for me?

**A. Yes.**

Q. Out loud.

**A. So "That study did not specifically examine whether antioxidant supplements were effective for the primary prevention of early AMD in people without signs of this condition."**

Q. It says "That study."

**A. Yes.**

Q. It's referring to the AREDS study; correct?

**A. It's referring to one of the AREDS publications which is Reference 22.**

Q. Go ahead and take a look at Reference 22 listed in Exhibit 2144.

**A. Yeah. So that is AREDS Report Number 8. There is a number of AREDS.**

Q. 1022.

**A. Yes. I want to make sure it's the same paper because they publish... so that's referring to the same paper, Paper Number 8.**

Q. Okay. So what Chong is saying is that the AREDS study that we've been discussing is examining a different population of patients than this population of people in need of primary prevention of early AMD; is that correct?

**A. So to get into -- to get into the AREDS study, you had to have disease and she's talking about patients who don't have any signs of the disease yet.**

Q. So when she's talking about primary prevention of early AMD, she's just saying that wasn't examined in the AREDS study; correct?

MR. FELDSTEIN: Objection. Misstates the reference.

**A. So that is what she's saying, yes.**

Q. And then at the bottom of the next paragraph, you see the sentence that ends, "The common perception is that a diet rich in antioxidants can protect against AMD."

**A. I see that phrase that the common perception is that a diet rich in antioxidants can protect against AMD.**

Q. You read the Chong reference as saying AREDS has a place in reducing the risk of progression of AMD in high-risk patients, but it just hasn't answered the question of whether it's effective for primary prevention of early AMD in people without signs of this condition?

MR. FELDSTEIN: Object to form and foundation.

**A. Well, that is what I'm taking from the abstract of the study, that those patients were not study -- you know, were not reported upon in AREDS Publication Number 8.**

Q. Okay. I'd like to talk about dosing of vitamin A and vitamin A equivalents. So I think earlier we agreed that the RDA for vitamin A is just under 1 milligram per day; is that correct?

**A. 900 micrograms for males and a little bit less for females, yes.**

Q. And I don't want to get hung up on the units, but 900 micrograms is about .9 milligrams; is that right?

**A. That is correct, yes.**

Q. And actually, you had mentioned before when we were looking for the AREDS reference, you went to Exhibit 1008 first, and so if I can, I just want to ask you about the dosing in that reference. Can you pull up 1008?

(Exhibit 1008, previously marked.)

Q. You have Exhibit 1008 in front of you?

**A. Yes, I do.**

Q. Now, before I ask you about the dosing, so I asked you some questions earlier about a date in September 2007.

**A. Okay.**

Q. Do you know why I keep asking you about September 2007?

MR. FELDSTEIN: Object to the form.

**A. Yes, I do.**

Q. And September 2007 is the date that we're evaluating for purposes of obviousness of the patent at issue; is that fair?

**A. Okay.**

Q. I mean, do you agree with me?

MR. FELDSTEIN: Object to the form.

**A. That's my understanding of the importance of that date.**

Q. Okay. So now Exhibit 1008, I just want to start with what I think is an easy question. At the front of the page, on the left-hand topside, right next to the numerals 43, it says, Publication in the Patent Gazette at January 18, 2007; correct?

**A. It does say that, yes.**

Q. And you reviewed Exhibit 1008 as part of formulating your opinions in this case; is that correct?

**A. Yes, I did review the exhibit.**

Q. When you reviewed Exhibit 1008, did you consider that it was -- that the information contained in it is prior art to the claims of the patent at issue?

MR. FELDSTEIN: Object to form.

**A. I recognize that the publication in the Patent Gazette is at an earlier time point, yes.**

Q. And I don't mean to -- you said you are not a legal expert, and I'm not asking you to be a legal expert, but you understood when you were engaging in this process of making your declaration that information that is published before September

2007 counts as prior art information against the patent that is challenged here; correct?

**A. I understand the importance of the 2007 date, yes.**

Q. Go ahead. Using your own words, tell me what is the importance of that September 2007 date and whether something is published before it or not.

**A. It has to do with whether it's in prior art, yes. And I'm not an attorney, but there are multiple dates on patents, you know, when the provisional is filed, when it's converted, when it's filed internationally, so that's why I'm trying to be a little bit careful about how to answer that. But I do recognize that there is a date in which something would be considered prior art.**

Q. Just to hopefully maybe make things easier, do you have the patent in front of you as well?

**A. I can retrieve the patent, quickly, yes. Okay. I have the patent.**

Q. So on the front page of the patent, left-hand column, next to -- there is a number that says 60 in parentheses, and it says, "Provisional

application" and it has a number, and it says "filed on September 12, 2007."

Do you see that?

**A. I'm seeing a November 3rd, 2016.**

Q. So that's the filing date next to 22; correct?

**A. Which line are you on?**

Q. So this application was filed November 3rd, 2016, and then if we go further down, there is a line that says "PCT filed September 12, 2008."

Do you see that?

**A. Yes. I do see that.**

Q. And the 2008, that's earlier than the 2016; correct?

**A. Earlier than 2016? Yes.**

Q. And then if we go back even further next to the line 60 down below, do you see the number 60 in parentheses?

**A. Yes.**

Q. And there it says "Provisional application number." Do you see that?

**A. Yes. 60/993,379.**

Q. Right. And that's says "Filed on September 12, 2007."

**A. Yes, I see that.**

Q. And that's -- I'm not going to hold you to this, but that's the earliest date you see on the face of the patent here; right?

MR. FELDSTEIN: Object to the form. Misstates the reference.

**A. There is a file date that's earlier than that.**

Q. What are you referring to?

**A. No, that is the earliest. That's 2016. No, that's 2016. Yes, I do see that.**

Q. Okay. So the earliest date is nine years before the filing date of this actual patent; right?

**A. The filing date is 2016 versus 2007 is nine years, yes.**

Q. And so this September 12, 2007, that's the date that we're worried about when we're making our obviousness analysis here; is that correct?

MR. FELDSTEIN: Object to form, foundation.

**A. I understand that's the date you're referring to, yes.**

Q. Is that the date that you used for your opinions?

**A. That date was the date that I considered.**

Q. Okay. Let's go back to Exhibit 1008, just keeping that 2007 date in mind.

**A. Okay.**

Q. So we're back at Exhibit 1008, and you agree that Exhibit 1008 was published before the 2007 critical date?

MR. FELDSTEIN: Object to form and foundation.

**A. Yes, I do.**

Q. And I just want to make sure. I don't think you did anything like this, but you didn't, like, exclude Exhibit 1008 from the prior art for this patent and just pretend it's not prior art, did you?

MR. FELDSTEIN: Object to form.

**A. I recognized that it was published in 2007. That is the publication date.**

Q. So when you were performing your analysis, you accepted that Exhibit 1008 is prior art that is relevant for determining whether the claims of a challenged patent are obvious; is that fair?

MR. FELDSTEIN: Objection. Objection to form and foundation.

**A. I did consider that, yes.**

Q. And you agree that the Exhibit 1008 -- I'm going to withdraw that question and start over.

When you considered Exhibit 1008 as prior art to the claims at issue, did you do that grudgingly; are you doing it under protest; is that something you disagree with, but you are just forced to do it, or do you agree that it's prior art that should be considered when you are determining whether the claims at issue are obvious?

MR. FELDSTEIN: Object to form and foundation.

**A. So I'm not an attorney and I think the definition of prior art is a legal definition, but this publication date is prior to the date on the patent '045 that we're talking about.**

Q. Okay. So now I'm going to ask you about the dosing.

**A. Okay.**

Q. So here on the very first page, just in this, sort of the first list of ingredients that shows up in the patent, it gives a dosage of 0.1 milligrams to 2 milligrams of vitamin A; is that correct?

**A. Yes, that is correct.**

Q. And that basically sort of encompasses a range right around the middle of which is the RDA for vitamin A; is that fair?

**A. The recommended daily allowance is in the middle of that range, yes.**

Q. Let's look at page 2, in the right hand column, top of the page.

**A. Okay.**

Q. So once again, they have the same range of .1 to 2 milligrams of vitamin A that centers on the recommended daily allowance of vitamin A; correct?

**A. Yes.**

Q. And in there they also have, they say, in addition to that 0.1 to 2 milligrams of vitamin A, they say, additionally you may have 6 to 32 milligrams of carotenoids; do you see that?

MR. FELDSTEIN: What paragraph are you on?

MR. MILLS: Paragraph 8, right-hand column, page 2.

MR. FELDSTEIN: Object to form. Misstates the document. And thank you.

**A. Okay, so I just read that paragraph.**

**Can you repeat the question?**

Q. So in addition to the individual receiving 0.1 to 2 milligrams of vitamin A, the reference also teaches 6 to 32 milligrams of carotenoids; correct?

**A. There is a list of multiple ingredients. That dose of vitamin A is included, and down at the bottom they also mention secondary plant compounds selected from the group comprising of -- and they mention a few items there, including 6 milligrams to 32 milligrams of carotenoids comprising carotenoids selected from the group that include beta-carotene, lutein, zeaxanthin and lycopene.**

MR. FELDSTEIN: Read slower for the reporter, please.

THE WITNESS: Sorry. I can reread that, that's fine.

**A. So on the upper right-hand column, they list the dose that ranges from 0.1 to 2 milligrams of vitamin A, and then at the end of that list, they also mention, "secondary plant compounds selected from the group comprising 6 milligrams to 32 milligrams of carotenoids comprising carotenoids selected from the group comprising beta-carotene, lutein, zeaxanthin and lycopene." And then they**

**start mentioning flavonoids and other things, yes.**

Q. So that range of 6 to 32 milligrams of carotenoids, kind of in the middle of that is the 15-milligram dose of beta-carotene that was used in the AREDS study; right?

**A. So 15 milligrams of beta-carotene would fall within those borders, yes.**

Q. So if we are talking about the vitamin A and the beta-carotene used in the AREDS study by patients who were taking the treatment combination and Centrum vitamin, that is consistent with what the Ortho Pharma reference is saying in paragraph 8, where it says you can have .1 to 2 milligrams vitamin A and also you can have 6 milligrams to 32 milligrams of carotenoids including beta-carotene; correct?

MR. FELDSTEIN: Object to form and foundation.

**A. So it's consistent with the dosage that is described in the Ortho Pharma patent document.**

Q. Thank you. On the third page, in paragraph 19, there is a preferred range of vitamin A that's given.

Do you see that?

**A. Okay. I see line 2.**

Q. So the preferred range of vitamin A that's in paragraph 19 of Exhibit 1008 is 0.4 milligrams to 1.1 milligrams; correct?

**A. Yes. That is correct.**

Q. Those are essentially the recommended daily allowances of vitamin A for children ranging up through adults; is that correct?

**A. I'm not familiar with the dose of vitamin A that's recommended in children. For the adult ranges that fall within these brackets that are listed in section 19, second indentation down.**

Q. Now I direct your attention to page 5 of Exhibit 1008, to paragraph 36.

**A. Okay.**

Q. Paragraph 36 gives a wider range of vitamin A treatment than what we looked at before; correct?

**A. Are you referring just to vitamin A or all of them?**

Q. To the vitamin A.

**A. Yes. The vitamin A dosages described in paragraph 36 are broader than the ones we were just talking about.**

Q. And here the preferred range is 1.7 to 5 milligrams of vitamin A; is that correct?

**A. The preferred range is 1.7 to 5 milligrams of vitamin A, correct.**

Q. Now, this may be an unfair question, but I don't mean to be unfair, I'm going to ask you about international units.

Is international units of vitamin A something that you are comfortable testifying about?

**A. That depends on what you ask me.**

Q. We can start simple.

**A. Okay.**

Q. So just in general, what's an international unit when we are talking about vitamin A?

**A. So the milligrams or grams or micrograms refers to the weight of something, meaning you literally just take it, put it on a scale, how much does it weigh. The international units refers to the activity, which is more complicated. So, for example, you could have an enzyme that has very low activity and you can have an enzyme that has very high activity and the weight might not accurately reflect what the activity actually is. You might need something like an international unit to measure it.**

Q. Okay. And as a general matter, do you -- do you know how to convert international units of vitamin A to milligrams of vitamin A?

**A. So there is a conversion factor. I don't know offhand what the number is for vitamin A, but you'd look up a conversion factor and essentially do the division.**

Q. Does it sound right that it's something like you take the international units, multiply it by 0.3 and that gives you the micrograms of vitamin A?

**A. It's different for different vitamins, so I'd have to really look that up or look at one of the references. I don't recall that number to be honest with you.**

Q. So without trying to get too bogged down in the math --

**A. Okay.**

Q. -- there are situations in which prior to September 2007 people have administered doses that are larger than about 1 milligram RDA of vitamin A to patients with retinal diseases; do you agree with me?

MR. FELDSTEIN: Object to form and foundation.

**A. Can you repeat that for me?**

Q. So prior to September 2007, there are cases where people have been administered doses of vitamin A that are larger than the approximately 1 milligram RDA when those patients have retinal diseases?

MR. FELDSTEIN: Object to form and foundation.

**A. Vitamin A has been administered to patients, including with retinal diseases, and I'd have to know the exact conversions to know if that was higher than that or not.**

Q. So first let's just start with the retinal diseases. What are the retinal diseases where prior to September 2007 patients were being administered vitamin A?

**A. Well, I mean, there was a clinical trial for retinitis pigmentosa. Eliot Berson was the first author on that trial so that had vitamin A administered.**

**There were other trials that were tried before the actual mechanism of Stargardt disease was known. People tried a variety of things, you know, for Stargardt's before it was recognized that it was actually a problem with vitamin A handling.**

**In fact, to my memory, there were a small clinical trial that looked at supplementing Stargardt patients at that point with vitamin A. It's in one of the exhibits that I reviewed. That would been before the gene defect was actually identified.**

Q. I think you mentioned three things; I want to see if I have them correct. So the first one I heard is that, and you mentioned the Berson, B-e-r-s-o-n, reference, administered vitamin A to treat retinitis pigmentosa; is that right?

**A. That's one of them, yes.**

Q. And then you also mentioned, I think -- did you mention Sorsby?

**A. I did not mention Sorsby, no.**

Q. Is Sorsby a disease in which it's ever happened that people administered vitamin A to patients with Sorsby on this?

**A. I'd have to go through the references to check. I'd have to have the references checked.**

Q. So then there is a second one, though, at least that at some point people were administering vitamin A supplements to Stargardt patients; is that correct?

**A. My recollection is that there was a small trial, I'd like to go through it and find the**

**original document on it, that did not see a beneficial effect actually.**

Q. So that was before 2007 they gave vitamin A to Stargardt patients; is that correct?

**A. Before 2007.**

Q. With the retinitis pigmentosa in Berson, do you recall what dose was administered?

**A. I'd have to look. I think it was 15,000 units. But I'd have to find the original reference. I have to find the reference, I have to find the exhibit number. Page 64. Berson is 1040. And the reason I remember it, it was 15,000 international units a day of vitamin A.**

**(Exhibit 1040, previously marked.)**

Q. Do you have any rough way to equate 15,000 units into milligrams.

**A. I can't do it without knowing the conversion factor, unless it's stated in the paper.**

Q. I don't think this necessarily gives you the conversion factor, but starting on page 771 of Exhibit 1040, on the left-hand column, the second full paragraph. It starts with "We observed."

Do you see that?

**A. Yes. They are comparing it to the diet which was 3,600 units per day.**

Q. Okay. So what they say here is, "We observed no toxic side effects of vitamin A supplementation of 15,000 international units per day for four to six years in our study patients who had an average intake of vitamin A by diet of about 3,600 international units per day." It refers to a table. Correct?

**A. That is what they say, yes.**

Q. So they are telling us there that these patients had, on average, 18,600 international units of vitamin A every day for four to six years and they observed no toxic side effects; is that correct?

**A. That's correct for the average intake. But because it's coming from the diet, you don't know what the doses are in the individual patients, but that is correct from the averages.**

Q. And just to be clear, the dose from the supplement was kept constant, but people, their daily intake from diet might vary somewhat; is that correct?

**A. Yes.**

Q. If we look at the table which I think shows up on page 766.

**A. Okay.**

Q. There for the dietary intake of vitamin A they give us a plus or minus value for each group; is that correct?

**A. They give a plus or minus, yes.**

Q. What is the plus or minus value, not numerically, but what does it signify?

**A. Usually the standard deviation.**

Q. So most of the patients had a dietary vitamin A intake of pretty close to the 3,600 that they identify on page 771; correct?

MR. FELDSTEIN: Object to the form.

**A. I mean, if that's one standard deviation, which it probably is, then 67 percent of the patients fell within 1 standard deviation and 95 percent would have fallen within 2 standard deviations of that, of the average. So there would be outliers, but the standard deviation is given.**

Q. Okay. So I want you to take a minute just to -- well, I'm going to see if we can find the conversion factor, but I don't think it's here.

**A. Okay.**

Q. I'll see if I can find one.

I guess let me ask you, though, under the comment on page 770, it says, "The present study supports the hypothesis that a 15,000 international

units supplement of vitamin A taken daily will slow the progression of the common forms of retinitis pigmentosa as monitored by ERG testing."

Do you see that?

**A. I do see that sentence, yes.**

Q. And further down there is a sentence that says "Survival and mean change analyses."

Do you see that sentence?

**A. "Survival and mean change analyses on the subgroup of patients"?**

Q. Yes. It says that that analysis showed that those receiving vitamin A at 15,000 international units per day retained more retinal function than those who were receiving vitamin A at only 75 international units per day; correct?

**A. It does say that, yes.**

Q. And in the next sentence, it says that the rate of decline for group A was significantly slower than the rate of decline for the trace group; correct?

MR. FELDSTEIN: Objection. Misstates the reference.

**A. It does say, starting in the middle of the sentence, "also showed that the rate of decline for group A, 8.3 percent per year, was**

**significantly slower than the rate of decline for the trace group, 10.0 percent per year."**

Q. Taking a look at page 771, in the right-hand column, the very last paragraph, you see where it says, "In summary, based on ERG results, the course of retinal degeneration in retinitis pigmentosa was slower on average among patients receiving a daily supplement of 15,000 international units of vitamin A than the course of those not taking this dosage."

**A. I do see that sentence, yes.**

Q. Then the very last sentence of the paragraph, you see where it stays, "Based on these findings and the analysis of decline of ERG amplitude as a function of total vitamin A intake, it is recommended that most adult patients with the common forms of retinitis pigmentosa take a supplement of vitamin A, 15,000 international units per day, under the supervision of an ophthalmologist," and it goes on to talk about vitamin A.

**A. Yes, I do see that.**

Q. Thank you. You can set that aside.

So I asked you about Sorsby's fundus. So you discuss in paragraph 132 of your declaration --

**A. Paragraph 132?**

Q. Yes. You see there you reference the Jacobson reference, so that's Exhibit 1041.

**A. I do see the reference to 1041.**

Q. Okay. Is Exhibit 1041 one of the references that you considered in coming to your opinion?

**A. Yes, 1041 is one of the references I considered.**

**(Exhibit 1041, previously marked.)**

Q. So looking at the abstract in Exhibit 1041, do you see it says vitamin A at 50,000 international units per day was administered orally?

**A. I do see that sentence in the abstract, yes.**

Q. And we can look back at Berson if you need it, but in Berson, it was 15,000 international units; correct?

**A. Yes, it was 15,000.**

Q. So here it's three times more than Berson; correct?

**A. It's more than three times more than Berson, yes.**

Q. And also, not to get too up in the math,

but remember the dietary intake was about 3,600.

**A. Yes.**

Q. So the amount that they were giving in Berson was about four times as much as they were getting from their diet; right?

**A. Yes.**

Q. And here, we have three times more than that; is that correct?

**A. Yes.**

Q. So in Jacobson, there is -- roughly 12 times your dietary intake of vitamin A is additionally being given to these Sorsby fundus patients; is that correct?

MR. FELDSTEIN: Object to form and foundation.

**A. The Sorsby fundus dystrophy patients are receiving much more vitamin A. It would be 50,000 divided by about 3,600.**

Q. So I have to add it's almost 14 times?

**A. 14.**

Q. And for the Sorsby fundus, that's being administered orally; is that correct?

**A. Yes. It says orally.**

Q. And in Berson, the vitamin A also is being administered orally; correct?

**A. I'd like to look at Berson again, but I believe so. But I prefer to look at it again. 1040?**

**Yes, in Berson, they are putting it into soft gelatin capsules and advised to take one capsule daily at breakfast.**

Q. And so in Berson, we have about four times the daily intake. In Jacobson, we have about 14 times the daily intake, okay. And I'm not going to hold you to these numbers and pretend that they are precise, but we are just trying to have a rough idea, and because .9 is harder to multiply than 1. Okay?

**A. Okay.**

Q. So let's just pretend for a moment that that 3,600 dietary intake, let's pretend that they were getting about the recommended daily allowance. I'm not asking you to agree that that's what they were getting, but just for our purposes, and let's pretend that it is 1, 1 milligram, because that's easy.

So do you understand the hypothetical?

**A. I do, yes.**

Q. So if we assume that in Berson through their diet people are getting about 1 milligram of

vitamin A, in Berson they were giving them an extra dose of about 4 milligrams of vitamin A; correct?

MR. FELDSTEIN: Object to form. Incomplete hypothetical.

**A. It's roughly four times.**

Q. And with those same assumptions in Jacobson were getting about 14 milligrams of vitamin A as a supplement; correct?

MR. FELDSTEIN: Object to form. Incomplete hypothetical.

**A. They were getting a ratio of about 14 to one, yes.**

Q. So if we -- so we'll just stop there. This gives us a ballpark at least. So I think that's helpful.

Okay. So looking at this Jacobson reference, on the left-hand column of the first page, the bottom paragraph, you see where it says, "A testable hypothesis about mechanism in SFD is that the subretinal deposit acts as a diffusion barrier for entry of sufficient vitamin A into the photoreceptors."

Do you see that?

**A. I do see that sentence, yes.**

Q. My first question is: SFD refers to

Sorsby's fundus dystrophy; correct?

**A. Yes, that does refer to it.**

Q. What is Sorsby's fundus dystrophy?

**A. So Sorsby's disease is an inherited retinal degeneration, very rare. The gene mutation that actually causes the disease has been identified in a couple of families, and it's a gene mutation, it's something called TIMP, T-I-M-P dash 3, which stands for Tissue Inhibitor of Matrix Metalloproteinase. So essentially it's an enzyme that degrades the extracellular matrix, because the matrix turns over constantly, and there was a defect in that enzyme in patients with this disease.**

Q. How is this disease -- let me limit my question now to prior to September 2007.

Prior to September 2007, how was Sorsby fundus diagnosed?

**A. So the disease is diagnosed on the basis of patient symptoms which is usually decreased visual acuity and night blindness, advanced retinal imaging which essentially involves taking a photograph of the retina, which includes a normal color photograph and also something called an autofluorescence photograph, which is kind of like**

**taking a picture of something with a black light where all you see is a fluorescent material and you don't see the underlying structure.**

**There are other tests that we do in the office commonly including an angiogram test called a fluorescein, f-l-u-o-r-e-s-c-e-i-n, angiography and optical coherence tomography or OCT.**

Q. Okay. So here in the Jacobson references, they are postulating that there may be a diffusion barrier that is keeping the vitamin A from entering the photoreceptors to participate in the visual cycle and that that is causing the night blindness that is associated with Sorsby fundus dystrophy; correct?

**A. That is what they are postulating, yes.**

Q. The very next sentence, do you see where the reference is vitamin A is a critical part of the visual cycle?

**A. I do see that sentence, yes.**

Q. Do you agree with that portion of the sentence that we both just read out loud?

**A. I agree that vitamin A is a critical part of the visual cycle.**

Q. Do you see the sentence goes on to say, "Deficiency in vitamin A is well known to cause

night blindness and eventual death of photoreceptors"?

**A. Yes, I do see that.**

Q. Do you agree with that portion of the sentence?

**A. Yes, I do.**

Q. And you agree that that was known to a person of ordinary skill in the art prior to September 2007?

**A. Yes. I mean, this paper was in 1995.**

Q. So earlier we talked about vitamin A had been administered prior to September 2007 to retinitis patients and Stargardt patients.

Are you now comfortable adding Sorsby fundus to the list?

**A. This study was before 2007. Yes, I am.**

Q. So now I want to make a comparison of these doses and of course the dose that we have is rough. There is a little bit of estimating there.

If we are talking about a 4-milligram dose in the Jacobson -- sorry, in the Berson reference -- I'm going to start my question over so I get it right.

My question is actually going to be in the Ortho Pharma, so can you pull back up Ortho

Pharma.

**A. Yes, the number of that was --**

Q. 1008.

**A. Okay.**

Q. And we were on paragraph 36.

**A. Okay. I'm at paragraph 36.**

Q. Okay. And then kind of just to summarize, the first vitamin A doses in Ortho Pharma were kind of centered around the RDA; correct?

**A. Yes.**

Q. And now in this paragraph 36, they've given a wider range that has this preferred, gets up to kind of about 2 to 5 milligrams of vitamin A; correct?

**A. They preferred that it's between 1.7 and 5 milligrams.**

Q. So this range in paragraph 36 of Ortho Pharma is more consistent with the Berson dose of vitamin A, which we thought is about 4 milligrams; is that correct?

MR. FELDSTEIN: Object to form. Misstates the reference.

**A. I mean, this is all milligrams, not in units. But the 4 milligrams is between 1.7 and 5.**

Q. Okay. Let's look at paragraph 43 of Ortho Pharma.

**A. Paragraph 43.**

Q. So here the dose is much lower. It's 600 micrograms; right?

**A. 600 micrograms is written there, yes.**

Q. For vitamin A?

**A. For vitamin A, yes.**

Q. So in paragraph 43, this is perhaps consistent with the RDA for an adult woman; is that correct?

MR. FELDSTEIN: Object to form.

**A. It's a little bit below that. For adults, it's 700 for women, roughly, and about 900 for men.**

Q. So in paragraph 36, where the range went up to 9 milligrams, that dose still does not exceed what we expect the Jacobson dose was that was used for the Sorsby fundus dystrophy; correct?

MR. FELDSTEIN: Object to form. Misstates the reference.

**A. So the Jacobson dose was 50,000 international units. The conversion factor we didn't look up, but we deduced it from the Berson paper, and that's how we came with our 14**

**calculation. So that 14 is higher than the 9 milligrams. But there may be other numbers in the literature for the conversion units. But it is higher.**

Q. Are you ready for a break?

**A. Excuse me.**

Q. Are you ready for a break?

**A. Yeah, I can take another break. Sure. That's a good idea actually.**

**(Recess taken from 12:26 p.m. to 12:34 p.m.)**

**(Exhibit 2150, previously marked.)**

BY MR. MILLS:

Q. Doctor, do you have Exhibit 2150?

**A. 2150, yes, I do.**

Q. Is Exhibit 2150 one of the references that you relied upon for your declaration?

**A. Yes.**

Q. Looking under the Introduction, there is a discussion about dietary vitamin A; do you see that?

**A. I see the sentence that starts with the dietary vitamin A, yes.**

Q. Then there is a sentence that says, "Up to 75 percent of dietary vitamin A in Europe, the United States, and other industrialized nations is

preformed vitamin A, which is largely derived from multivitamins, fish liver oil, and the fortification of foods such as milk, butter, margarine, breakfast cereals, and some snack foods."

**A. Yes, I see that.**

Q. So you agree that in the United States, Europe and other industrialized nations, it's a common practice to fortify milk, butter, margarine, breakfast cereal and some snack foods with preformed vitamin A; correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. Let me just read that paragraph again for a moment.**

**(Pause.)**

**A. Okay. I'm sorry, can you repeat the question.**

Q. Do you agree with Exhibit 2150 that in the United States, Europe and other industrialized nations that it's a common practice to fortify milk, butter, margarine, breakfast cereal with preformed vitamin A?

MR. FELDSTEIN: Objection, foundation.

**A. I mean, the statement says what it says. I don't have any way of verifying its inaccuracy. It basically just says that in industrialized nations preformed vitamin A is largely --**

THE REPORTER: Doctor, I'm sorry, please say that again.

**A. I don't have any independent way of verifying it, but the sentence, you know, says what it says, and it says, in industrialized nations, preformed vitamin A is largely derived from multivitamins, fish liver oil, and fortification of foods such as milk, butter, margarine, breakfast cereal and some snack foods.**

Q. Do you disagree with Exhibit 2150 and about what it says in that sentence?

MR. FELDSTEIN: Object to form, foundation.

**A. I don't disagree with it. I just don't have any way of verifying it. They are pulling it from a secondary source, which is a Reference 1 and 2, and I just don't have any way of verifying the source they are pulling it from.**

Q. In preparing your opinions and your declaration, you didn't consider whether or not the United States and Europe and other industrialized

nations commonly fortify milk, butter, margarine, breakfast cereal and some snack foods with preformed vitamin A?

**A. I did not verify that statement that's in this paper.**

Q. Now I'm going to ask you about provitamin A carotenoids, okay?

**A. Okay.**

Q. Remember, we talked about provitamin A carotenoids before?

Do you know approximately the number of provitamin A carotenoids that exist in the food supply?

**A. I do not know that number, no.**

Q. In our discussions earlier, you identified a prominent one for us; do you remember that?

**A. Beta-carotene is a provitamin carotenoid, yes.**

Q. And it's a prominent provitamin A carotenoid that is commonly obtained through the diet; correct?

MR. FELDSTEIN: Object to form.

**A. It is a common provitamin A carotenoid that's in diet, yes.**

Q. Do you see right after the numbers 3, 4 --

**A. Okay.**

Q. -- on this page of Exhibit 2150, it says, "The cleavage of provitamin A carotenoids to retinal is a highly regulated step."

Do you see that?

**A. I do see that, yes.**

Q. Do you agree with that statement?

**A. I mean, the body has a way of regulating this, and I don't doubt that this would be a regulated step.**

Q. The reference says "a highly regulated step." Are you disagreeing with Exhibit 2150 that cleavage of provitamin A carotenoids to retinal is a highly regulated step?

MR. FELDSTEIN: Object to the form and foundation.

**A. I would say that, you know, for me to agree to that during a deposition, I'd have to see what the regulation is, because "highly" is an adjective that can be a little vague. So as a scientist, I would want to look, and see a chart almost, of oral carotenoids versus vitamin A cleavage to see how tightly regulated that is.**

Q. Let me kind of ask you the inverse question.

**A. Okay.**

Q. Are you offering an opinion in this case that the cleavage of provitamin A carotenoids to retinal is not a highly regulated step?

MR. FELDSTEIN: Object to the form.

**A. I'm offering an opinion that it is regulated and how tightly regulated, I just don't have the data to put that extra word in there.**

Q. And when Exhibit 2150, and we are discussing the cleavage of provitamin A carotenoids, that includes beta-carotene; correct?

MR. FELDSTEIN: Objection, foundation.

**A. So beta-carotene is a provitamin A carotenoid, so it would include that.**

Q. That sentence goes on to say, "Vitamin A toxicity from provitamin A sources is largely impossible."

Do you see that?

**A. I do see that sentence.**

Q. Do you disagree with Exhibit 2150 when it says that vitamin A toxicity from provitamin A sources is largely impossible?

MR. FELDSTEIN: Object to the form.

**A. So it's unclear from that sentence whether they are referring to the provitamin A carotenoids which are listed above which are naturally-occurring products in plants or whether they are referring to all the provitamin A sources that are out there.**

Q. And does that make a difference as to whether you agree or disagree with this statement?

**A. So to agree to that statement as a scientist, this is the person's individual interpretation, whoever the authors are, yes, this is what they have written down and they don't reference it. I don't doubt it, but to agree to this as a scientist, I really kind of need to see data. Data to me would be a table of a range of input, you know, like orally administered or people eating a certain amount of provitamin A carotenoids, and then the thing on the vertical axis and the Y axis would be liver stores of vitamin A or circulating vitamin A, something like that, to agree with that statement. I don't doubt that as human beings we have a way of regulating this.**

Q. Okay. You are not offering an opinion

one way or the other agreeing or disagreeing with the statement in Exhibit 2150 that vitamin A toxicity from provitamin A sources is largely impossible?

MR. FELDSTEIN: Object to form.

**A. I don't have enough data to say if it's largely impossible or not.**

Q. You do agree that as of September 2007, a person of ordinary skill in the art would have had available to them this statement in Exhibit 2150 that vitamin A toxicity from provitamin A sources is largely impossible; correct?

**A. You are asking me if I agree that prior to 2007 somebody could have seen and had access to this statement? Yes, this paper was published in 2006.**

Q. And when Exhibit 2150 says, "Vitamin A toxicity from provitamin A sources is largely impossible," the provitamin A sources that they are referencing includes provitamin A beta-carotene; correct?

MR. FELDSTEIN: Object to form and foundation.

**A. It would include -- this is where it's unclear if they are referencing the provitamin A**

**carotenoids in plant foods. If they are just talking about provitamin A carotenoids in plants, then beta-carotene would be a part of that and would be included.**

Q. Do you have any interpretation of that sentence that would exclude beta-carotene?

MR. FELDSTEIN: Object to form.

Q. Let me withdraw that question and ask a different question.

Are you interpreting that sentence, that vitamin A toxicity from provitamin A sources is largely impossible, to exclude beta-carotene from the provitamin A sources for which vitamin A toxicity is largely impossible?

**A. No. I think they are including beta-carotene from plant sources, from plant foods. Whether they mean to include beta-carotene from any other source, I don't know.**

Q. Thank you. Take a look on page 2 of this exhibit, right-hand column, at the very last paragraph, there is an "eg" followed by a number 50,000 international units, bracket, 15,000 retinol equivalents per day for a 60 kilogram man.

Do you see that?

**A. I do see that, yes.**

Q. So does this give you information about how to calculate international units into milligrams?

**A. It does give you some information on that, yes.**

Q. Is this conversion information consistent with the rough calculations we were doing before?

**A. I just would like to read the paragraph for just a moment.**

**(Pause.)**

**A. Okay. I'm sorry, can you repeat the question?**

Q. So I'm asking you whether this conversion of 50,000 international units to 15,000 retinol equivalents, whether that's consistent with the rough conversion that we did before.

**A. Well, they introduced a new term, unfortunately, which is the retinol activity equivalent units, as opposed to just simply milligrams of vitamin A. So I think I want to be careful about the relationship between those two.**

**If you assume that that is one to one, then the answer to your question would be yes. But I can't tell from this if that's really one to one or not.**

Q. And this reference does confirm what you told us, that the recommended daily allowance of vitamin A for men is 900 micrograms of retinol activity equivalent per day; correct?

**A. Well, the RDA for men is 900 micrograms of vitamin A, so if the amount of vitamin A or retinol and the retinol activity equivalent are identical, then that would be correct.**

Q. So these two sentences here seem to answer the question that a retinol activity equivalent is essentially a microgram of retinol; is that fair?

**A. I think if it is one, then the numbers all match up, but I don't think they are really defining the retinol activity equivalent in this. I have to go back to the original source.**

Q. This reference is from 2006; is that correct?

**A. Yes. This is published in 2006.**

Q. And to your knowledge, in 2006, the recommended daily allowance of vitamin A in men was 900 micrograms of retinol; correct?

**A. I actually don't know what it was in 2006, but it would have to be looked up to ensure that it really has not changed, which these usually**

**do not change very much.**

Q. So you don't have any reason to doubt, looking at this, that when it says 900 micrograms retinol activity equivalents per day that that is the same RDA as the 900 micrograms of retinol RDA that you were already aware of from vitamin A; correct?

MR. FELDSTEIN: Object to form.

**A. I don't have any reason to doubt, but I'd want to actually look this up and verify that that was correct.**

Q. Accepting that conversion for the moment, you would agree that 50,000 international units of vitamin A would amount to 15 milligrams of retinol; correct?

MR. FELDSTEIN: Objection, form. Incomplete hypothetical.

**A. Can you repeat that?**

Q. Accepting that 900 micrograms of retinol activity equivalents is 900 micrograms of retinol, you agree that 15,000 retinol equivalents is 15 milligrams of retinol?

MR. FELDSTEIN: Object to form.

**A. So just to verify, you said 50,000 international units or did you say 15,000?**

Q. I'm trying to take it step by step. I don't mean to be confusing. So my first question is about the 15,000 retinol equivalents. So that 15,000 retinol equivalents represents 15 milligrams of retinol; correct?

MR. FELDSTEIN: Object to the form.

**A. Assuming the first part of your statement, that assumption about the relationship between activity units and milligrams, that would be roughly correct, yes.**

Q. So based on what we can see here, which you'd like to confirm if we had the data, but it seems plausible to you that 50,000 international units of vitamin A is 15 milligrams of vitamin A; correct?

MR. FELDSTEIN: Object to form.

**A. That would seem plausible.**

Q. So this is a little bit more math, but I promise not to spend a long time on math, but 50,000 is about 15 milligrams and 100,000 is about 30; correct?

**A. Okay.**

Q. You agree at least so far as the math?

**A. Yes.**

Q. Our assumptions are still the same as

before; right?

**A. Okay.**

Q. Now we are going to double it again. So now if I'm talking about 200,000 international units, that is 60 milligrams of vitamin A; correct?

MR. FELDSTEIN: Object to form.

**A. Okay.**

Q. You agree that that's what the number would come out to?

**A. Yes. You multiply everything by 4, yes.**

Q. And just for completeness, if we're talking about 300,000 international units, that's 90 milligrams of vitamin A; correct?

MR. FELDSTEIN: Object to form.

**A. Okay.**

Q. You agree with the math?

**A. I agree with that multiplication part, yes.**

Q. Okay. Please take a look at page 197 of Exhibit 2150.

**A. Okay. 2150. That may be the same paper we're on.**

Q. Yes.

**A. Okay.**

Q. So on the left-hand column, the first

paragraph under vitamin A supplementation, the second sentence, it says, "The benefits of supplementation with high doses of preformed vitamin A in combating vitamin A deficiency in women and children are documented."

Do you see that?

**A. I do see that, yes.**

Q. And then in the second paragraph down there, it says, "The World Health Organization currently recommends that lactating women in developing nations be given large doses of preformed vitamin A to reduce the incidence of deficiency both in themselves and in their nursing infants."

Do you see that?

**A. I do see that, yes.**

Q. The very next sentence says, "Currently, the International Vitamin A Consultative Group recommends two doses of 200,000 international units vitamin A administered at least 24 hours apart as soon after delivery as possible."

Do you see that?

**A. I do.**

Q. So using our conversions from before, the women give birth, and as soon as possible on day

one, they get 60 milligrams of vitamin A, and then 24 hours later they get another 60 milligrams vitamin A; correct?

**A. Yes.**

Q. And then in the next line, it says that there were recent trials of one dose each of 300,000 and 400,000.

Do you see that?

**A. Yes, I do.**

Q. So in the 300,000, they are getting a 90-milligram dose one day and then a 90-milligram dose the next day; correct?

**A. Can you say that again?**

Q. So when they are giving 300,000 international units in two doses, that's 90 milligrams of vitamin A one day and then 90 milligrams the next day?

MR. FELDSTEIN: Object to the form.

**A. It's possible. I'm reading that a little differently. "Recent trials of one dose each of 300,000 and 400,000 IU were conducted in Africa."**

Q. Okay, I think I understand what you're saying.

**A. I think that's just one dose.**

Q. Okay. So here they are doing a single

90-milligram dose instead of two 60-milligram doses; correct?

**A. Correct, I think so.**

Q. But they are also giving in a single day a single dose of 120 milligrams?

**A. Yes.**

Q. On the right-hand side, in the middle of the page, there is a paragraph that says "Roy, et al."

Do you see that?

**A. I do.**

Q. And it has an N equals 50; do you see that?

**A. Yes, I do.**

Q. What do you understand the N equals 50 to mean?

**A. N would be the number of patients that were treated.**

Q. Okay. So here they gave 60 milligrams of vitamin A to 50 women; is that correct?

**A. Let me read that paragraph again.**

**(Pause.)**

**A. They are saying there were 50 women treated, but some of them received placebo after delivery, so I can't tell if it's -- if they**

**counted the placebo. Typically they do. And whether the randomization was one to one. So it might have been 25 treated women and 25 placebo, but you can't really tell.**

Q. Vitamin A was administered orally; correct?

**A. Single oral dose, yes.**

Q. Further down, there is another study where the N equals 300; correct?

**A. I see the N equals 300.**

Q. And here they are giving them a 60-milligram dose; correct?

MR. FELDSTEIN: Object to the form. Misstates the document.

**A. I'd like to read that sentence.**

**(Pause.)**

**A. Okay. Can you repeat the question for me.**

Q. So here they are giving 60 milligrams of vitamin A in a study where the N value was 300; correct?

MR. FELDSTEIN: Objection to form.

**A. So the N value was 300, but the women received either the 200,000 units of vitamin A or they received placebo. And again, you can't tell**

**the randomization, but these are typically one to one.**

**(Mr. Neer left the room.)**

**A. So it's possible that half the women received the vitamin A. That would be the most common design.**

Q. In the next paragraph, here the number of women is 924; correct?

**A. Okay. So they did have 924 women, yes.**

Q. And in this study, they are also administering the 60-milligram dose of vitamin A?

MR. FELDSTEIN: Object to form.

**A. Yes, they are giving the 200,000 units.**

Q. Thank you. Do you have Exhibit 1042?

**A. I do have 1043.**

Q. 42. 1042.

**A. I do have 1042.**

**(Exhibit 1042, previously marked.)**

Q. Is this one of the references that you considered in coming to your opinions in this case?

**A. Yes.**

Q. And sorry, I should have asked this before, but you probably won't have to turn back, but that last exhibit, 2150, you agree that that information was available to a person of ordinary

skill in the art before September of 2007?

MR. FELDSTEIN: Objection, form, foundation.

**A. Let's look and see when it was published. 2150?**

Q. Yes.

**A. Penniston is the first author?**

Q. Yes.

**A. Yes, that was published in 2006.**

Q. Thank you.

Okay, back to 1042.

**A. Okay, I'm there.**

Q. If we look at the abstract under Purpose, it says, "Previously, we reported the results of a Phase III placebo-controlled trial in 2,297 randomized participants with moderately severe actinic keratoses wherein 25,000 international units per day vitamin A caused a 32 percent risk reduction in squamous cell skin cancers."

Do you see that?

**A. Yes.**

Q. And using our math that we've been discussing, the 25,000 international units is about 7.5 milligrams; correct?

MR. FELDSTEIN: Object to the form.

**A. I hate to agree to something without writing it down and looking at it myself, but the 200,000 units was 60 milligrams; correct?**

Q. Yeah.

**A. Okay. So the 100,000 units was 30 milligrams. Okay. So this is 25,000 units, which would be 7.5 milligrams.**

Q. Thank you.

**A. Okay.**

Q. So the reference then says, "We hypothesized that dose escalation of vitamin A to 50,000 or 75,000 international units per day would be both safe and more efficacious in skin cancer chemoprevention."

Do you see that?

**A. I do.**

Q. Those doses, the 50,000 dose is the 15-milligram dose, and the 75,000 international units would be about 22.5 milligrams; correct?

**A. Yes.**

Q. Under the experimental design, do you see that the patients received these three doses, 7.5, 15, or 22.5 milligrams of vitamin A for 12 months?

**A. Yes, I do see that.**

Q. And they made a comparison to placebo; is

that correct?

**A. Yes.**

Q. And under Results, you see it says that there is no significant difference in expected clinical and laboratory toxicities between the groups of participants randomized to placebo, 7.5 milligrams, 15 milligrams or 22.5 milligrams of vitamin A per day?

**A. I do see that, yes.**

Q. And under the Conclusions, do you see it says that vitamin A doses of 15 and 22.5 milligrams per day for one year proved safe and equally more efficacious than the 7.5 milligram per day dose and can be recommended for future skin cancer chemo preventative studies?

**A. I do see that, yes.**

Q. Under the Introduction, the first paragraph, the last sentence of the paragraph says, "Having previously shown that vitamin A doses as high as 300,000 international units per day were well tolerated for up to one year in patients with advanced cancers."

Do you see that?

**A. I see that sentence, yes.**

Q. That 300,000 international units per day

corresponds to approximately 90 milligrams of vitamin A per day; correct?

MR. FELDSTEIN: Object to form.

**A. Yes.**

Q. Thank you. You can set that document aside.

**A. Okay.**

Q. Do you have Exhibit 2155 -- actually, before we move on, I keep doing this, I'm very sloppy.

For Exhibit 1042, you agree that that information would have been available to a person of ordinary skill in the art as of September 2007?

MR. FELDSTEIN: Object to form and foundation.

**A. So that article would have been available in 2007. It was published in 2004.**

Q. So yes?

MR. FELDSTEIN: Object to form and foundation.

Q. Dr. Del Priore, so you agree that the information we discussed in Exhibit 1042 would have been available to a person of ordinary skill in the art by September 2007?

MR. FELDSTEIN: Object to form and

foundation.

**A. Can you repeat the Exhibit Number?**

Q. 1042.

MR. FELDSTEIN: Same objections.

**A. So 1042 is the paper by Alberts, et al, and it was -- the publication date is March 15th of 2004, so yes.**

**(Exhibit 2155, previously marked.)**

Q. Thank you.

Now let's move on to Exhibit 2155.

**A. 2155?**

Q. Yes. Exhibit 2155 is a reference that you considered in coming to your opinions in this case?

**A. Yes, it is.**

Q. Please take a look at the last page of the article, page 943.

**A. Okay, I'm looking at the last page of the article.**

Q. The first full paragraph on page 943, it says, "A significant difference in cholesterol concentrations between the retinol and placebo groups was observed in the present study."

Do you see that?

**A. I see that sentence, yes.**

Q. The next sentence says, "Cholesterol concentrations in the retinol group were relatively stable throughout the study."

Do you see that sentence?

**A. I see that sentence.**

Q. What do you understand that phrase "Cholesterol concentrations in the retinol group were relatively stable throughout the study" to mean?

**A. Well, they don't really define the term "relatively stable." I like to look at mathematical numbers, but it basically means just that, they were relatively stable. I always like to go back and look at the original data.**

Q. So the sentence goes on to say, "In contrast with a steady decline in concentrations in the placebo group, resulting in a 2 to 3 percent difference in cholesterol concentrations between the retinol and placebo groups."

Do you see that?

**A. I do see that.**

Q. So this Exhibit 2155 is telling us that the group that received vitamin A, their cholesterol basically stayed the same and for some reason in the placebo group, their cholesterol went

down.

MR. FELDSTEIN: Object to form.

Q. Is that correct?

**A. The sentence does state -- essentially does state what you just said, that there was a steady decline in concentration of the placebo. And in the other group that was treated, it was basically relatively stable, and that resulted in a 2 to 3 percent difference in the cholesterol concentrations between the retinol and placebo groups.**

**(Exhibit 2154, previously marked.)**

Q. Thank you. You can set that document aside.

Do you have Exhibit 2154.

**A. I do have Exhibit 2154.**

Q. And this is an exhibit that you relied upon in forming your opinions?

**A. Yes.**

Q. Please take a look at the very first -- the very first paragraph on the first page, the last two sentences of that paragraph.

Do you see that? Do you see it says, "This study is a tour de force in experimental design, execution, and statistical analysis"

**A. I do see that sentence, yes.**

Q. And then also on the first page of Exhibit 2154, in the very first full paragraph, the last sentence says, "The investigators deserve congratulations on the successful completion of this ambitious, rigorous and interesting study."

Do you see that?

(Mr. Neer reentered the room.)

**A. I see that sentence, yes.**

Q. And here they are referring to the Berson study that we talked about earlier; is that correct?

**A. Yes, I do think they are referring to that.**

**(Exhibit 2153, previously marked.)**

Q. Thank you. You can put that document aside.

Do you have Exhibit 2153.

**A. I do have 2153, yes.**

Q. Please take a look at page 2 of Exhibit 2153, the right-hand column, the very first sentence of the second paragraph says, "This study was meticulously designed and extraordinarily well performed, and it represents an important scientific contribution."

Do you see that?

MR. FELDSTEIN: Misstates the reference. Objection.

**A. I see that part of the first sentence.**

Q. And that is a statement by Michael F. Marmor?

**A. The first part of that sentence, this is a paper written by Michael F. Marmor.**

Q. And when Michael F. Marmor says, "This study was meticulously designed and extraordinarily well formed, and it represents an important scientific contribution," he's referring to the Berson study that we discussed previously; correct?

**A. He is referring to the Berson study, yes.**

Q. Looking now at page 3 of Exhibit 2153.

**A. 2152?**

Q. 53. 2153. Same document.

**A. Okay.**

Q. So page 3, on the right-hand side, next to the big B, the first sentence says, "Based on the findings reported recently in the Archives by Berson, et al."

Do you see that?

**A. I do see that.**

Q. That's referring to the Berson reference

that we discussed previously; correct?

**A. Yes, it is.**

Q. And it says, "The National Retinitis Pigmentosa Foundation and the RP Foundation Fighting Blindness have begun national campaigns that will probably persuade most patients with retinitis pigmentosa to begin a lifelong regimen of vitamin A supplementation."

Do you see that?

**A. Yes. I just want to make sure I understand something. You are asking me if I agree with the sentence or if I see the sentence?**

Q. I'm asking if you see the sentence.

**A. I do see the sentence, yes.**

Q. And then turn to page 4 of Exhibit 2153.

**A. Okay.**

Q. Do you see on the right-hand column, there is a horizontal line that says "In reply"?

**A. I see "In reply" on the right-hand column, yes.**

Q. So do you agree that the words that follow under the bar that says "In reply" are responding to criticisms or questions about the Berson study?

MR. FELDSTEIN: Object to form,

foundation.

**A. So my version of this cuts off in the middle of the paragraph, so I can't even tell who wrote this.**

Q. Yes, so that actually was going to be my next question. My version too. It looks like they submitted just one side of the story, the criticisms but not the complete response; is that what you are seeing?

MR. FELDSTEIN: Object to the form.

**A. I'm seeing an incomplete response with no signature at the end of this paragraph.**

Q. But if we look at the very first paragraph under "In reply," it says, "We are pleased by the interest generated by our article in the June 1993 issue of the Archives and welcome the opportunity to reply."

Do you see that?

**A. I do see that, yes.**

Q. Is it fair to infer this is a reply from the authors of the Berson paper?

MR. FELDSTEIN: Objection, calls for speculation, form.

**A. It appears to be a reply, because they say "our article," and it would be a lot easier if**

**we could see the rest of it.**

Q. So it appears to you that the authors to the Berson article were replying to the criticisms in Exhibit 2153, but that those -- the complete version of the reply was not included in the exhibit; correct?

MR. FELDSTEIN: Object to form, foundation.

**A. That appears to be the author's reply, yes.**

Q. Thank you. You can set that document aside.

(Whereupon, the witness was excused and a luncheon recess was taken at 1:20 p.m.)

- - -

AFTERNOON SESSION

1:57 P.M.

LUCIANO VITO DEL PRIORE, M.D., Ph.D.,
having been previously duly sworn and/or affirmed, testified further on his oath as follows:

EXAMINATION

BY MR. MILLS (continued):

Q. Earlier, we talked about some of the anatomy of the eye; do you recall that?

**A. Yes, I do.**

Q. We were talking about the RPE. We talked about the outer segments of the photoreceptor cells; do you recall that?

**A. Yes.**

Q. You talked about some of the blood-retina barrier?

**A. Yes.**

Q. What is the Bruch's membrane?

**A. So the Bruch's membrane is a structure called a basement membrane, and it's essentially beneath the RPE or beneath the retinal pigment epithelium. It's actually the surface that the RPE**

**cells attach to. So you have the cells sort of in the middle, and then you have the blood vessels underneath them, and in-between the blood vessels and the RPE is the Bruch's membrane.**

Q. What is the function of the Bruch's membrane?

**A. So it does a couple of important things. The main thing is that it -- it regulates the morphology or what the cells look like of the pigment epithelium, and it has to have a couple of very, very important properties. So number 1, it has to let molecules go through it. It has to act like a porous sieve basically because molecules are going to go from the blood supply area, the choroid, to the pigment epithelium, and they have to be able to traverse or go across the basement membrane.**

**Number 2, the basement membrane serves as an anchoring point, because in order for the RPE cells to remain as a single layer, as a monolayer, they actually have to be stuck to a surface to be organized that way. If they are not adherent -- if they are not stuck or adhered to something, they won't be organized in that fashion.**

**So with a proper functioning Bruch's**

**membrane, just like a proper subfloor, all your tiles are nice, they are very even, they have constant space in-between them. They have grout holding the whole thing together. On the other hand, if Bruch's membrane is damaged, then that whole structure sort of starts to fall apart.**

Q. You agree that there are certain retinal dystrophies that are associated with a thickening of the Bruch's membrane; correct?

**A. Yes. Some of the retinal dystrophies are associated with thickening of the Bruch's membrane.**

Q. Can you identify which ones?

**A. Well, I mean, the best example is probably age-related macular degeneration, so that's a condition in which one of the first things that actually happens is that the basement membrane or Bruch's membrane gets thicker as a function of age. That becomes clinically significant for patients in their 50s. Although, interestingly, on autopsy studies, you see some change in Bruch's membrane even happening in 20- or 25-year-olds, but it doesn't really become important until patients are much older.**

Q. You mentioned the difficulty of small molecules diffusing through the Bruch's membrane

when it thickens.

Do you recall that?

**A. Well, when Bruch's membrane starts to have damage, a variety of things happen, including the fact that it becomes a barrier for molecules to move across it.**

Q. One of the molecules that have difficulty diffusing through a thickened Bruch's membrane is vitamin A; is that correct?

**A. Theoretically, a lot of molecules will have trouble going through. Whether a molecule has trouble going through or not has to do with the size, whether it needs a, something called a transport protein to move it across. So for example, a small molecule can go across Bruch's membrane very easily, even in disease, but if it has to be carried by something, it has to be carried, you know, by a tank or by a truck, then it doesn't get through very well.**

**And then the second thing that's important is how soluble the molecule is in water and in oil, because as molecules move through the back of the eye from one layer to the other, they are going to carry -- encounter different barriers, and some molecules can -- are very water soluble.**

**They can just sort of stay in the liquid part and move across very quickly, but a lot of molecules are not very water soluble and they need to be transported. It's complicated.**

Q. You agree that Sorsby's dystrophy is associated with the thickening of the Bruch's membrane?

**A. Sorsby's dystrophy is definitely associated with changes in Bruch's membrane. I mean, the disease is caused by a protein that is necessary for maintaining Bruch's membrane.**

Q. You agree that Malattia Leventinese --

**A. Pretty good. Malattia Leventinese, the Italian pronunciation, M-a-l-a-t-t-i-a, I think, and L-e-v-a-n-t-e-s-e? I probably got the spelling wrong. What was the question?**

Q. It's also associated with the thickening of the Bruch's membrane?

**A. It's associated with the abnormalities in Bruch's membrane.**

Q. So you were talking about AMD earlier being associated with the thickening of the Bruch's membrane. So in some ways because of that thickened membrane, material is having trouble getting through from the circulating blood supply

into the retina; is that fair?

**A. The difficulty encountered in transport would be -- would move in both directions actually, yes.**

Q. Ultimately one of the things that the body does to address this thickened Bruch's membrane in an advanced stage of AMD for instance is that the blood vessels push their way, force their way through the Bruch's membrane and create exudative AMD; is that correct?

**A. Well, so exudative or wet macular degeneration is characterized by blood vessels breaking through Bruch's membrane. The stimulus for it is not really well-known. And it may be a compensatory or compensation mechanism for molecules not being able to go across, but I would say the science in that is incomplete.**

**There are a variety of theories, including just that the blood vessels start invading this thick basement membrane because there is not enough oxygen getting to the retina or the stimulus is actually not known.**

Q. The ultimate effect, though, of this exudative AMD is a return of the flow of nutrients from the circulatory system towards the retina; is

that correct?

**A. So it's -- I don't know if that's really known. The pathology of why people start developing blood vessel growth in this area is not known and whether that's the body trying to repair, you know, trying to solve a basic problem, the basic problem being that the basement membrane is too thick, molecules can't get across it, so you just go ahead and try to move the blood vessels a little bit closer. It's an interesting idea. I don't think that's uniformly accepted.**

Q. Is there also a role in lipofuscin in thickening or blocking the flow of material through the Bruch's membrane?

**A. So lipofuscin is largely, although not exclusively, contained within the pigment epithelium, you know, within the cells themselves. There are certainly deposits that patients get on -- in the basement membrane in Bruch's membrane, so you sort of have this fluorescent material present in a couple of different places. So the fluorescence is largely is intracellular. We know this because when people lose those cells, which you can see in some of our imaging, the fluorescence, the glow in the dark, affect the**

**cells, the cells just go dark. There is some fluorescence from Bruch's membrane itself implying that there is probably abnormal material that is glowing in the dark, if you will, a fluorescing in that basement membrane. Whether it's the exact same chemical composition, is not clear.**

Q. Can you take a look at Exhibit 2074.

MR. FELDSTEIN: I don't want to interject or interrupt, but I think that one might be missing from the binder.

THE WITNESS: 2074?

MR. MILLS: Yes.

MR. FELDSTEIN: It might be there. I don't think it is.

THE WITNESS: I don't see it. What is 2074?

MR. MILLS: Rattner 2006.

THE WITNESS: Okay. I've seen Rattner. Is there another number?

MR. FELDSTEIN: Jad has a copy for you.

THE WITNESS: Okay.

MR. MILLS: I'll come to the rescue here.

MR. FELDSTEIN: Thanks.

THE WITNESS: Thank you.

(Exhibit 2074, previously marked.)

BY MR. MILLS:

Q. I actually have a guess as to why you don't have 2074 in your binder, and this actually almost threw us through a loop too because in your declaration instead of calling it 2074, you call it Rattner 2006. So that's probably why they missed it in your binder. They were searching for that exhibit number or the exhibit numbers didn't come up.

**A. Okay.**

Q. I was curious why you call it "Rattner 2006" without the exhibit number in your declaration. Is there something that you -- you know, is that just something that didn't get ironed out before the declaration was filed? Or is this a reference that is near and dear to your heart that you just referred to by the author's name because it's one you already were familiar with?

**A. I think neither one. I recall reviewing this, so I've reviewed this before. I'm not sure why the number is not there in the declaration.**

Q. Okay. And for this exhibit, Rattner 2006, which is Exhibit 2074, is this an exhibit

that you were familiar with before you worked on this case?

**A. Is this an exhibit that I was familiar with --**

Q. Before you worked on this case.

**A. No. I mean the senior author is a person I'm familiar with, but I don't know that I have reviewed this paper in detail.**

Q. Okay. I'm going to step back and ask sort of a broader question as well: Out of all of the exhibits that are discussed in your declaration, can you tell me any of those that are ones that you reviewed before you began work on this case?

MR. FELDSTEIN: Object to form.

**A. I mean, I read the scientific literature. It would be a bit challenging to go through all of them and tell you which ones, but I was familiar with the general scientific field, which would have included a lot of these references but not all.**

Q. And understanding that you are not going to recall everything, but just tell me any references that you do recall as you sit here, or ones in the case that you walked on the case already familiar with?

**A. You are asking which references I was familiar with before the case?**

Q. Yes.

MR. FELDSTEIN: Object to form.

**A. I'd really have to go through them individually to answer that properly.**

Q. The Berson reference?

**A. Definitely.**

Q. The AREDS study publication?

**A. Yes.**

Q. Are there any others that stand out in your mind?

**A. Excuse me?**

Q. Any others that stand out in your mind?

**A. I'm sure there would be, but I'd have to go through them to answer that properly.**

Q. Jacobson?

**A. Yes. The Jacobson paper I was familiar with.**

Q. Anything else that as I'm mentioning these, is this jogging your memory?

**A. No, those are all yeses, but to answer that question without going through the references would be difficult.**

Q. I understand. So Rattner 2006, please

take a look at 863.

**A. Okay.**

Q. So in the left-hand column, the last paragraph before it says "Dominant Stargardt-like macular dystrophy," there is a sentence that begins "A2E forms."

Do you see that?

**A. I do see that.**

Q. It says, "A2E forms by non-enzymatic reactions in photoreceptor outer segments and RPE phagolysosomes apparently as a minor and unavoidable byproduct of the retinoid cycle."

Do you see that?

**A. I do see that sentence, yes.**

Q. So you agree that A2E is a minor and unavoidable byproduct of the retinoid cycle?

**A. Do I agree with that sentence? I don't think I would use the word "minor" in that.**

Q. Do you agree that A2E is an unavoidable byproduct of the retinoid cycle.

**A. I don't think I would have inserted the word "minor" or "unavoidable" if I was writing that.**

Q. You do agree that A2E is a byproduct of the retinoid cycle?

**A. I do, yes.**

MR. FELDSTEIN: Let him fully finish the question.

**A. Yes.**

Q. And when it says "retinoid cycle," is that synonymous with the visual cycle?

MR. FELDSTEIN: Object to form. Foundation.

**A. Can you repeat that for me?**

Q. When it says A2E is a byproduct of the retinoid cycle, is that saying A2E is a byproduct of the visual cycle?

MR. FELDSTEIN: Object to form and foundation.

**A. So I do think that's what they are referring to, yes.**

Q. That's the same visual cycle we were talking about before, when there was an 11-cis-retinal and going through the different conformational changes; right?

**A. I think that's what they are referring to, yes.**

Q. So the visual cycle itself, all of those steps can happen, it's not essential to any of those steps that A2E form; is that what that means

when it says "byproduct"?

MR. FELDSTEIN: Object to form, foundation.

**A. So the visual cycle refers to the cycle part, the thing that looks like an oval or a circle, and it's for essentially bringing back the visual chromophore into its original native state. And then that side arm that's shown on the pictures where A2E is, is just that, it's a side arm, where the molecule reacts with phosphatidylethanolamine, which is a lipid, which is present in cells. It accounts for a significant amount of the lipid, and it basically goes along that pathway.**

Q. Okay. So when there is a cycle that's essential for vision and then the A2E arm is something that if you could cut off, it's not going to impact the vision cycle; is that correct?

MR. FELDSTEIN: Object to form and foundation.

**A. It should not impact the vision cycle.**

Q. Okay. And then in that paragraph up above, it's talking about ABCR function. It says, "Current evidence indicates that ABCR functions in the retinoid cycle to flip all-trans-retinal," and instead of saying the rest of the word I'm going to

say --

**A. Phosphatidylethanolamine adducts.**

Q. Okay -- "from the luminal to the cytosolic leaflet of the disc membrane, thereby facilitating reduction of all-trans-retinal to all-trans-retinol, an essential step in recycling the isomerized chromophore."

Do you see that?

**A. I do see that sentence, yes.**

Q. So converting all-trans-retinal to all-trans-retinol is an essential step in recycling the isomerized chromophore; is that correct?

**A. Yes, it is.**

Q. Okay. And back when we had a discussion about the outer segments, the chromophore exposure to light that converts the 11-cis-retinal to all-trans-retinal, that's taking place in the outer segments; correct?

**A. That is taking place in the outer segments, yes.**

Q. And then this ABCR is trying to pump the all-trans-retinal from the outer segments of the rods or cones into the RPE so that in the RPE the retinal can be recycled back into retinol; is that right?

**A. So the ABCR protein is crucial in that process. I'd like to read it again. My recollection is that it actually flips -- it flips it from the -- from one side of the membrane to the other is how it actually works.**

Q. I think they call it a flippase; is that a term?

**A. Correct.**

Q. But when it takes the all-trans-retinal to get into the flippase, it actually has to become N-RPE to go into the flippase; is that correct?

**A. Let me -- not my understanding, but let me reread this quickly.**

**(Pause.)**

**A. Okay. Do you mind asking the question again?**

Q. So when the protein that's coded by ABCR -- I think that protein is called Rim protein; is that correct?

**A. It's called the Rim protein, yes.**

Q. And Rim protein is a flippase that grabs a version of ATR from one side of the membrane and flips it onto the other side of the membrane; correct?

**A. It has to flip it from one side of the**

**membrane to the other, yes.**

Q. And what it grabs on the luminal side of the membrane is called N-RPE; is that correct?

**A. Can you say that last part again.**

Q. When the Rim protein grabs the all-trans-retinal in the luminal side, it's grabbing that all-trans-retinal in the form of N-RPE; correct?

**A. I'm not sure what N-RPE is.**

Q. So I think it's the all-trans-retinal phosphatidylethanolamine adduct, but let me know if you disagree.

MR. FELDSTEIN: Object to form.

**A. I'm not sure what the term is you are referring to.**

Q. Okay. Earlier, just a moment ago, you were talking about the conjugation of all-trans-retinal with a phosphatidylethanolamine.

**A. Yes.**

Q. Do you know what that's called when those two things are together?

**A. Well, if there is one, it's called -- there is a couple of them. Once there is two of them, that's what A2E is, and if there's only one visual chromophore, the abbreviation is ATR,**

**similar to the all-trans-retinoic acid, which is why it gets a little confusing.**

Q. So this PE conjugated all-trans-retinal, that's what the Rim protein flippase is grabbing to switch and flip over onto the cytosolic side of the membrane; correct?

**A. So the inversion or flipping that's going on is in something called the disc membrane, which is actually inside the cell, so it's a little bit different. So the photoreceptor cells have a stack of 50 to 100 discs inside them. They are called discs because they look like flat little frisbees. And each of those discs has an inside and an outside. So what happens is when light gets absorbed by 11-cis-retinal, the molecule gets released, the all-trans part, inside the disc, and has to come outside of the disc in order for it to get to the pigment epithelium, and that flippase is on the membrane and grabs it, and then basically flips it to the outside so it can then go to the pigment epithelium.**

**(Exhibit 2110, previously marked.)**

Q. Thank you. I think I can help out. If we look at Exhibit 2110 and keep the other one handy because I think we may go back and forth a

little bit.

**A. Okay.**

Q. Is 2110 in your binder?

**A. Yes. 2110 is in my binder.**

Q. Look at the second page of the document. It's page 76 of the reference.

**A. I'm there.**

Q. There is a heading that says The Pathophysiology of Stargardt Disease; do you see that?

**A. I do.**

Q. And then the second paragraph under that heading is describing this flippase activity that you're talking about; correct?

**A. I'd have to read the paragraph. Are you referring to the paragraph that says, "In a normal eye, a photon of light"?**

Q. Yes.

**A. Let me just read that for a moment.**

**(Pause.)**

**A. Okay. I've read the paragraph.**

Q. So this paragraph is describing the process we were discussing just a moment ago; correct?

**A. Yes, it is.**

Q. Okay. And you see the acronym N-RPE?

**A. Yes, I do see that.**

Q. So N-RPE is one way of calling this adduct when the all-trans-retinal is combined with the lipid phosphatidylethanolamine; correct?

MR. FELDSTEIN: Object to form.

**A. So that is the way they are using that very confusing abbreviation.**

Q. Okay. And I'm not trying to get bogged down in the abbreviations, but the point I want to make sure that we understand that we are clear on, to see if we have agreement about, is that when the Rim protein is grabbing the all-trans-retinal, the form in which it is grabbing it is this conjugated form with the lipid, the phosphatidylethanolamine; correct?

MR. FELDSTEIN: Object to form, foundation.

**A. So the chromophore, the all-trans-retinal, when it flips, it is -- I just want to make sure I understand what you are asking. You are asking if it's bound to phosphatidylethanolamine?**

Q. My question is about the Rim protein, it grabs all-trans-retinal when the all-trans-retinal

has been conjugated together with the phosphatidylethanolamine?

**A. I believe that's correct, yes.**

Q. And then this Exhibit 2110, it tells us that after it flips the N-RPE out of the disc space into the cytoplasm of the rods and cones, the Rim protein then cleaves the bond between the all-trans-retinal and the phosphatidylethanolamine; correct?

**A. That is what it says, yes.**

Q. So the way this protein is designed to work, it is designed to grab the N-RPE form, flip it over, and then when it flips it over, it releases -- it separates the two of them?

**A. I believe that's correct, yes.**

Q. Okay. And that allows the all-trans-retinal that's been flipped and then released to be reduced to all-trans-retinol and transported to the RPE so it can be recycled back into the visual cycle; is that correct?

**A. That is correct, yes.**

Q. Okay, great.

If you can please look back at Exhibit 2074, Rattner 2006.

**A. Okay.**

Q. And then in Figure 3, Figure 3 depicts at least a portion of the visual cycle -- actually, it shows the whole visual cycle; is that right?

MR. FELDSTEIN: Object to the form.

**A. I'd have to review this.**

**(Pause.)**

**A. Okay, I've reviewed the figure.**

Q. Okay. So Figure 3 depicts the visual cycle; correct?

MR. FELDSTEIN: Object to form.

**A. They are showing a part of the visual cycle. So, for example, that 11-cis-retinol in the middle column, they never show that going back to 11-cis-retinal bound to opsin. Maybe that's what that bar is over on the right. They don't show the enzymes. They don't show the carrier proteins. I think they are showing a part of it.**

Q. So it's a simplified version because it doesn't show you the enzymes that are doing it, but they start with -- well, I mean, it's a cycle, so where you start is a little bit arbitrary, but if we start with 11-cis-retinol on the bottom, it shows that being entered into the RPE; correct?

**A. It shows --**

MR. FELDSTEIN: I'm sorry,

objection. Misstates the record, form.

Q. It has an a arrow pointing from the 11-cis-retinol to the RPE; correct?

MR. FELDSTEIN: Objection. Same objections.

**A. I think it's confusing. The middle column might all be the RPE. It's a little confusing.**

Q. Okay. But it shows 11-cis-retinol becomes 11-cis-retinal and ends up bound to opsin in the photoreceptor; correct?

MR. FELDSTEIN: Object to the form.

**A. It does show -- sorry.**

MR. FELDSTEIN: That's okay.

**A. It does show that, yes.**

Q. And then it also depicts the formation of A2E as that arm, that side reaction you were talking about earlier; correct?

**A. It does show the formation of A2E, yes.**

Q. And the way it depicts A2E is that the A2E, it's an arm, it's a side reaction. It's not a necessary component of the visual cycle; do you agree?

**A. So that is correct. That is the way they are depicting it.**

Q. In the caption at Figure 3, on the left-hand column of the caption, the very bottom sentence there, it says -- it refers to A2E as an aberrant side product; do you see that?

**A. I do see the phrase "A2E, an aberrant side product," yes.**

Q. On the right-hand column of this page, the last paragraph that begins on that page, it says, "Current evidence suggests that at least some sub-RPE deposits have a dynamic natural history in which accumulation reflects a balance between deposition and clearance."

Do you see that?

**A. I see that sentence, yes.**

Q. Do you know what is meant by a balance between deposition and clearance of sub-RPE deposits?

MR. FELDSTEIN: Object to form and foundation.

**A. I'd like to read a little bit above and a little bit below that for a moment.**

**(Pause.)**

**A. Okay, I've read it. Do you mind repeating the question for me.**

Q. So in the bottom of the right-hand page

of 864 of Exhibit 2074, where it says, "at least some sub-RPE deposits have a dynamic natural history in which accumulation reflects a balance between deposition and clearance," do you have an understanding as to what that means?

**A. I have an understanding of what they are referring to, yes.**

Q. What is that?

**A. Essentially what they are meaning in my view from that sentence is if the sub-RPE deposits, which are proteins and lipids that are outside the cell, they're sort of wound up in the mortar underneath the cells, that those are dynamic and not static. If they were static, those deposits would be there and they would never resolve and the patient would accumulate other deposits, but the originals ones aren't going away.**

**What's actually seen in patients is a dynamic process where the deposits, which can be seen on photographs and OCT imaging, they are called drusen, d-r-u-s-e-n, that those can come and go and change over time. So patients can have deposits in one area, have a picture taken five years later, ten years later; some of those deposits are still there, some are gone, some new**

**ones have formed. And five years later the same part happens.**

Q. So drusen is one of the things that lipofuscin can be a component of; is that correct?

**A. So drusen fluoresce, what is actually fluorescing in the drusen is typically referred to as lipofuscin. Whether that's the exact same molecular molecule, the exact same molecule as what's fluorescing inside an RPE cell is unclear, but they are probably related to each other. Even if they are not identical, they are probably similar to one another.**

Q. So in Rattner 2006, when they are talking about there being a balance between deposition and clearance of the drusen, they are basically saying, your body can get rid of a certain amount of this. It doesn't necessarily stay in there forever, but if you are generating more of the drusen than you are getting rid of, it accumulates and causes a problem; is that fair?

MR. FELDSTEIN: Object to form. Misstates the reference.

**A. Well, that's really logical, but I don't know if it's true, believe it or not. And I say that because there are certainly -- there is**

**certainly literature that when you get resolution of drusen, sometimes you get atrophy, death of the cells exactly in the area where the drusen resolved. So what is clear is that the drusen are dynamic. They are not just, you know, stamped in a brick like an old Roman stamping and stay there forever. They really do come and go.**

**One would think that resolution of drusen is a good thing, but there certainly have been cases where in areas where there is large, especially confluent, meaning that they are all touching each other, drusen, that patients can develop atrophy in that area. So whether it's a good or bad process is unclear at this point.**

Q. So you agree that the Rattner 2006 reference raises at least the inference that lipofuscin-associated diseases like age-related macular degeneration, Stargardt disease may be homeostatic diseases in which the accumulation of the drusen has simply outstripped the ability of the body to clear the drusen?

MR. FELDSTEIN: Object to form.

**A. I don't think I can agree with that statement. I think what the Rattner paper says is just that the process is dynamic and why it's**

**dynamic, like why drusen even resolved is not very well understood. And on top of that, it's not really well understood whether that's beneficial or harmful.**

Q. Exhibit 2051.

**A. 2051?**

Q. Yes.

**A. I do not see 2051 in my folder.**

**Do you have a cross-reference for 2051?**

Q. It's not one that you have?

**A. No.**

**(Exhibit 2111, previously marked.)**

Q. Okay. What about 2111?

**A. Yes.**

Q. Is this a document that you considered and relied upon for your opinions in this case?

**A. Yes, it is.**

Q. Okay. On page 3 of the document, 2 to 3 --

**A. On page 3?**

Q. At the bottom of 2, let's start there. Do you see the very bottom of page 2 it says that A2E is a marker for RPE dysfunction?

**A. Are you referring to the legend?**

Q. On page 2 of Exhibit 2111, there is a

figure legend for Figure 2, and then beneath that, the article says -- so after the figure legend, it says, "The production of one such lipofuscin fluorophore."

Do you see that?

**A. I do see that, yes.**

Q. It says, A2E is a marker for RPE dysfunction.

Do you see that?

**A. I see that sentence, yes. Part of a sentence.**

Q. And it says, A2E is significantly associated with AMD pathogenesis; correct?

**A. Yes, that is what that says.**

Q. It says, "A2E is a downstream condensation product of all-trans-retinol with phosphatidylethanolamine."

**A. I see that, yes.**

Q. So before, the literature we were looking at said that A2E is a condensation product of all-trans-retinal with phosphatidylethanolamine; do you recall that?

**A. Yes.**

Q. Do you think here where it says "condensation product of all-trans-retinol with

phosphatidylethanolamine" is a typo?

MR. FELDSTEIN: Object to form. Calls for speculation.

**A. The ol and the al refer to the group at the end of the molecule. I'd have to look at the structure to see. You could probably get something like A2E from either the aldehyde or from the alcohol, and I don't know if that's the reason for the discrepancy in this or not. I don't know if that's a typo.**

Q. So if you read that sentence, the next sentence, it talks about all-trans-retinol being conjugated to PE within the disc membrane for transfer across the disc membrane by the transporter encoded by the ABCA4 gene.

Do you see that?

**A. Yes.**

Q. And then it says subsequent to that flipping, that now the all-trans-retinol -- it says, "subsequent conversion to all-trans-retinol."

Do you see that

**A. I do see that.**

Q. "By all-trans-retinol dehydrogenase."

Do you see that?

**A. Yes.**

Q. So what it literally says is the OL is going to be conjugated to PE, flipped over to the other side and be converted into OL.

Do you see that?

MR. FELDSTEIN: Object to form.

**A. Yes.**

Q. So when it's talking about OL being converted to OL, do you think that that's a typo? Do you think the first reference to OL is supposed to be AL?

MR. FELDSTEIN: Objection to form. Calls for speculation, foundation.

**A. So when light gets absorbed and it's 11-cis-retinal, which is going to be converted to all-trans-retinal, so it's going to start in the retinal form, bind to the phosphatidylethanolamine and then be flipped and probably converted to the OL later, I would think.**

Q. So this sentence here where it's talking about the OL conjugating to the PE and the OL being flipped and then the OL being converted to the OL, all of those references are -- they are typos, it should be AL is conjugating, being flipped and converted; is that correct?

MR. FELDSTEIN: Object to form and

foundation.

**A. This would make more sense if it started with the AL in that sentence than the way they are starting it with the OL.**

Q. And then on that page 3, the next sentence right after that says, "Conditions that favor increased levels of all-trans-retinol and decreased conversion to all-trans-retinol lead to accumulation of A2E."

Do you see that?

**A. Yes, I do.**

Q. So does that also seem to have in that first "all-trans-retinol," it seems like that's a typo, it should be AL; is that correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. I think that sentence would be enhanced by using "retinal" the first time that term is used.**

Q. So it should say, "Conditions that favor increased levels of all-trans-retinal and decreased conversion to all-trans-retinol lead to accumulation of A2E." Correct?

MR. FELDSTEIN: Object to form and foundation.

**A. So that sentence would make more sense if it was worded that way, yes.**

Q. Okay. Further down that page 3, where it says "Targeting Lipofuscin, A2E Formation," do you see that heading?

**A. I see the heading, yes.**

Q. It says, "Accelerated lipofuscin and A2E accumulation occurs in patients with AMD and Stargardt macular degeneration."

Do you see that?

**A. I do see that.**

Q. And then it says, "Accumulation of A2E has been associated with RPE dysfunction and atrophy and photoreceptor loss."

Do you see that?

**A. Yes, I do.**

Q. And then it says, "As such, recent efforts have centered on targeting A2E formation in RPE cells as a therapeutic strategy for AMD and AMD-like retinal disorders."

Do you see that?

**A. I do.**

Q. Do you agree with that statement?

MR. FELDSTEIN: Object to form.

**A. Do I agree with that statement now or the**

**state of the art in 2007?**

Q. Well, so let's start with: This is a reference from what year? This is from September 2006; is that correct?

**A. Yes, that is correct, 2006.**

Q. So as of the beginning of September 2007, you agree that a person of ordinary skill in the art would have been aware that recent efforts for treating AMD and Stargardt macular dystrophy have centered on targeting A2E formation in RPE cells as a therapeutic strategy for AMD and AMD-like retinal disorders; correct?

MR. FELDSTEIN: Object to form.

**A. Yes.**

Q. And then it goes on to say, early studies tried reducing dietary levels of vitamin A in order to do that.

Do you see that?

**A. What I see is, "In early studies, it was shown that reducing dietary levels of vitamin A, all-trans-retinol, inhibits lipofuscin and autofluorescence accumulation in the RPE."**

Q. The very next sentence says "impractical as a therapy."

Do you see that?

**A. I see "While impractical as a therapy," yes.**

Q. When it says "impractical as a therapy," it's referring to reducing dietary levels of vitamin A to inhibit lipofuscin and autofluorescence accumulation in the RPE; correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. So I believe that sentence is referring to reducing dietary vitamin A.**

Q. Right. So what this reference 2111 is telling us before September 2007 is that reducing dietary levels of vitamin A was impractical as a therapy for AMD and Stargardt macular dystrophy; correct? That's what it says.

**A. What it's telling us is that the observation was made that reducing dietary levels of vitamin A in these disorders, you know, inhibit both lipofuscin and the autofluorescence accumulation, but they judge that impractical as a potential treatment or therapy.**

Q. Thank you.

Turning to --

**A. Let me take my coat off for one second.**

Q. Yeah. So turning to the next page, below

the Figure 3, there is a discussion about Accutane; do you see that?

**A. I see the text below Figure 3, yes.**

Q. And Accutane is a brand name for a drug that's also called isotretinoin?

**A. That is correct.**

Q. Before this case, were you familiar with isotretinoin?

**A. Yes.**

Q. Have you ever prescribed isotretinoin?

**A. No, no. Not to my recollection.**

Q. Are you aware that there is a black box warning for the administration of isotretinoin?

**A. I don't recall ever prescribing it, but --**

Q. Aside from whether you've prescribed it or whether you had a kid, somebody you knew that had to take it or from any source of knowledge, are you aware that isotretinoin --

**A. I'm sorry, can you repeat that.**

Q. I'll withdraw the question and start a new question.

Regardless of whether you've ever prescribed isotretinoin, as you sit here today, are you aware that isotretinoin has a black box warning

accompanied with it?

MR. FELDSTEIN: Objection to form and foundation. Go ahead.

**A. I was not aware that it had a black box warning.**

Q. In reaching your opinions in this case, you didn't evaluate the FDA label describing the risks of administering isotretinoin; is that correct?

**A. Do you mind repeating that for me?**

Q. So as part of reaching your opinions in this case, you didn't evaluate the risks of administering isotretinoin that are listed in the FDA label for that drug; correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. I'm not sure what you're asking. If you can clarify one more time.**

Q. Did you look at the FDA label for isotretinoin in forming your opinions in this case so that you would know what the side effect and the contraindications are?

MR. FELDSTEIN: Objection to form and foundation.

**A. So I did not look at the FDA label.**

Q. Evaluating the complete set of contraindications and adverse events associated with the use of isotretinoin was not part of the analysis you did in providing your opinions in this case?

MR. FELDSTEIN: Objection to form and foundation.

**A. I did not look at the FDA label, which is different than asking if I'm aware of side effects of the medication. I'm not sure which one you are asking.**

Q. Did you do a complete analysis of the contraindications and adverse events associated with the use of isotretinoin before providing your opinions in this case?

MR. FELDSTEIN: Objection to form.

**A. I did not look at the FDA label so I did not do a complete --**

Q. Okay. Another question about Exhibit 2111.

**A. Okay.**

Q. Here, this isotretinoin and the Accutane, it says that it inhibits 11-cis-retinol dehydrogenase, the final step in regeneration of the visual chromophore.

Do you see that?

**A. I do see that, yes.**

Q. So going back to the visual cycle, the discussion that we had, this is the step in the visual cycle, this is the one that you studied previously in your work; correct?

**A. I'm familiar with the visual cycle, yes.**

Q. So because Accutane was known to inhibit 11-cis-retinol dehydrogenase, the final step in regeneration of the visual chromophore, it was predictable before September 2007 that the use of isotretinoin in patients with macular degeneration would lead to delayed dark adaptation and night blindness; correct?

MR. FELDSTEIN: Objection, form, foundation. Incomplete hypothetical. Excuse me.

THE WITNESS: Can I answer?

MR. FELDSTEIN: You can answer.

THE WITNESS: Can you ask it again, maybe break it down a little bit.

Q. Because it was known that isotretinoin inhibits 11-cis-retinol dehydrogenase, it was predictable that its use would lead to night blindness; correct?

MR. FELDSTEIN: Same objections.

**A. Because of where it inhibits in the visual cycle, there would be concern about potentially causing night blindness.**

Q. And because of where isotretinoin inhibits the visual cycle, it would have been predictable that it could result in delayed dark adaptation; correct?

MR. FELDSTEIN: Object to form. Foundation. Incomplete.

**A. I think that because of the words "inhibits the visual cycle" that one would be concerned about affecting dark adaptation adversely.**

Q. Here in Exhibit 2111, it says that the isotretinoin had been shown to reduce all-trans-retinal and subsequent formation of A2E products; correct?

**A. Can you point out to where you are in that section?**

Q. So I'm on page 4 in that first paragraph.

**A. Okay. I'd like to read the whole paragraph for a moment.**

Q. Okay.

(Pause.)

**A. Okay. Can you reask your question,**

**please.**

Q. So Exhibit 2111 conveyed prior to September 2007 that isotretinoin had been shown to reduce all-trans-retinal and subsequent formation of A2E products; correct?

MR. FELDSTEIN: Object to form. Misstates the reference.

**A. So that is what that sentence states.**

Q. It then goes on to say that the doses necessary to achieve these results in humans would be toxic.

Do you see that?

**A. It does say that, yes.**

Q. That information was conveyed to a person of ordinary skill in the art by September 2007; correct?

**A. The information that the doses necessary to achieve the results in humans would be toxic? I think there would be concern about toxicity. I don't know that the exact dose response curve was known, but you are interfering with the visual cycle, I think there would be concern.**

Q. In this statement here in Exhibit 2111, you are not disputing that a person of ordinary skill in the art by September 2007 would have

available to them this statement that doses necessary to achieve these results in humans would be toxic?

MR. FELDSTEIN: Object to form and foundation.

**A. So this paper was published in September of 2006. So a person of ordinary skill in the art would have this statement available to them.**

Q. Thank you. The same goes for, in the next paragraph, it says an alternative strategy was examined using fenretinide.

Do you see that?

**A. Yes, I do.**

MR. FELDSTEIN: Objection, misstates the reference.

Q. And it says that the patients treated with fenretinide reported effects on night vision.

Do you see that?

**A. On line 4, I see the following statement, "While this treatment has relatively few side effects, treated patients reported effects on night vision."**

**Is that the sentence you are referring to?**

Q. Yes.

**A. I see that sentence, yes.**

Q. So the effects on night vision, that refers to the night blindness; correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. I think there are many potential effects on night vision that don't have to go all the way to the severity of night blindness, and it's unclear there what effects they are talking about and what patients are reporting.**

Q. The adverse effects on night vision may also include delayed dark adaptation?

**A. Well, there are numerous changes that occur, but -- that is one of them, but it's not that exclusively.**

Q. Let's take a look at your declaration.

**A. Okay.**

Q. This is Exhibit 2192.

MR. FELDSTEIN: It's your separate binder, doctor.

THE WITNESS: It's one of these?

MR. FELDSTEIN: Your separate binder.

(Exhibit 2192, previously marked.)

Q. 2192 is the exhibit number.

**A. That's what I was trying to look for, but you want me to turn to a page of my declaration.**

Q. First I want to look at the first page of the declaration.

**A. At the first page, okay.**

Q. And confirm that that's Exhibit 2192.

**A. Okay. This is my declaration, yes. And it does have Exhibit Number 2192.**

Q. Okay. And look at the last page of your declaration.

**A. Okay.**

Q. Is that your signature there?

**A. Yes, it is.**

Q. Did you write it by hand or electronically?

**A. I don't recall if I wrote that by hand or electronically.**

Q. When you signed your declaration, had you had an adequate opportunity to attest to the truthfulness of the information in your declaration?

MR. FELDSTEIN: Object to form.

**A. Yes, I did.**

Q. As you sit here today, are there any corrections or retractions that need to be made in

your declaration?

**A. There are no retractions. I think I found an extra word in it, an extra retinyl word, which I don't recall where it is right now. But aside from that, no.**

Q. Please take a look at paragraph 284 of your declaration.

**A. Okay. I'm on 284.**

Q. Go ahead and take a moment to read it to yourself.

(Pause.)

**A. Okay.**

Q. In paragraph 284 you testify that isotretinoin, also known as Accutane, was considered too toxic for long-term administration in humans.

Do you see that?

**A. Yes, I do.**

Q. Do you stand by that testimony?

**A. Yes.**

Q. You also testified that the danger of side effects in humans, such as birth defects in pregnant women and depression and suicide reported in many cases of isotretinoin treatment would preclude long-term therapy with this drug.

Do you see that?

**A. I do see that, yes.**

Q. And you cite the Wolf 2003 reference for that?

**A. I do.**

Q. You agree that that information was available to a person of ordinary skill in the art before September 2007; correct?

**A. I do. The Wolf paper was 2003.**

Q. And you stand by this testimony?

**A. Yes, I do.**

Q. Please take a look at paragraph 285.

**A. Okay.**

Q. Go ahead and read it to yourself.

(Pause.)

**A. Okay.**

Q. In paragraph 285, you rely on a 2005 reference by Radu for the proposition that fenretinide was known to cause delayed dark adaptation and other side effects.

Do you see that?

**A. Yes, I do.**

Q. Do you stand by that testimony?

**A. Yes, I do.**

Q. You also rely on a 2004 reference by

Puduvalli for the proposition that patients treated with fenretinide experienced a variety of symptoms including seizure and confusion.

Do you see that?

**A. Yes, I do.**

Q. You agree that all of these side effects would have been known to a person of ordinary skill in the art prior to September of 2007?

**A. Yes, I do.**

Q. You stand by that testimony?

**A. Yes, I do.**

Q. Please take a look at paragraph 75 of your declaration; read it to yourself.

**A. Paragraph 75?**

Q. Yes.

**A. Okay.**

Q. In support of this paragraph, you cite a 2003 reference and a 2006 reference; correct?

**A. Yes, I do.**

Q. So here in paragraph 75 you testify that before September 2007 a person of ordinary skill in the art would have been aware that long-term slowing of the visual cycle leads to photoreceptor cell death and loss of vision; correct?

**A. Yes.**

Q. Do you stand by that testimony?

**A. Yes, I do.**

Q. Let's go back one paragraph, paragraph 74. Please read it to yourself.

**A. Okay.**

**(Pause.)**

**A. Okay.**

Q. In this paragraph, you cite 2001 references as well as a 2005 reference.

Do you see those?

**A. Yes, I do.**

Q. And you cite those references as teaching before September 2007 that slowing down the visual cycle causes delayed dark adaptation and night blindness; correct?

**A. Yes, that's correct.**

Q. Do you stand by your testimony in paragraph 74 that before September 2007 a person of order ordinary skill in the art would have known that treatment with isotretinoin or fenretinide will -- can slow down the visual cycle causing delayed dark adaptation and night blindness?

MR. FELDSTEIN: Object to form.

**A. Yes.**

Q. Please take a look at paragraph 277 of

your declaration.

**A. Okay, I'm at 277.**

Q. So in paragraph 277, you discuss Syfovre; correct?

**A. Syfovre.**

Q. And you also discuss Izervay?

**A. Yes.**

Q. You agree that both Syfovre and Izervay were approved by the FDA for the treatment of AMD?

**A. Yes, they were both approved.**

Q. And when the FDA approved these two drugs for the treatment of AMD, they did so based on their conclusion that these two drugs were both safe and effective for the treatment of AMD; is that correct?

MR. FELDSTEIN: Object to form and foundation.

**A. They approved the basis on efficacy and safety as part of their decision-making, yes.**

**(Exhibit 1066, American Academy of Ophthalmology Article, C5 Inhibitor Avacincaptad Pegol for Geographic Atrophy Due to Age-Related Macular Degeneration, Jaffe, et al., marked for**

**identification.)**

BY MR. MILLS:

Q. I'm handing you what has been marked as Exhibit 1066.

MR. FELDSTEIN: I'm going to reserve objections including its authenticity. I'm going to object and then reserve -- excuse me, I'm going to object including for authenticity, relevance and reserve other objections.

Q. Do you recognize this document?

**A. Yes, I recognize this.**

Q. Is this a document that you reviewed in the past?

**A. Is it a document that I've reviewed in the past? Yes, I've reviewed this in the past.**

Q. When you reviewed it, was that part of your work in this case or part of your regular clinical practice?

**A. The second one.**

Q. When did you review this article?

**A. I reviewed it when it was published and I've read it since then. So I've read this article previously.**

Q. Please take a look through the article sufficient for you to tell me whether this article

appears to be an authentic version of the article that you reviewed in the past.

**A. Okay.**

MR. FELDSTEIN: Objection to form and foundation.

(Pause.)

**A. Okay.**

Q. Are there any indications there that call into question for you the authenticity or reliability of this version of this document?

MR. FELDSTEIN: Objection to form and foundation.

**A. I don't see anything that would lead me to think that it was not authentic.**

Q. What journal is this published in?

**A. The journal it is published in is Ophthalmology. It's a professional journal for our academy.**

Q. It was published in 2020?

MR. FELDSTEIN: Object to form and foundation.

**A. The publication date is in 2021, yes.**

Q. This is a reputable journal in the field?

**A. Yes.**

Q. This is a peer-reviewed article; correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. Yes, it is.**

Q. Earlier, we talked about the purpose of peer review; do you recall that?

**A. The question is?**

Q. Earlier, we talked about the purpose of peer review?

**A. Yes.**

Q. So this article went through the rigorous peer review before it was published; is that correct?

**A. Yes. This article should have gone through peer review, yes.**

Q. This is a large randomized placebo-controlled study; correct?

MR. FELDSTEIN: Object to form.

**A. It's a randomized clinical trial, sham-controlled, with 286 patients in it.**

Q. And you used the word "sham-control," is that different than placebo control?

**A. Well, yes. It's a little bit different and the reason for it is that it's an interventional trial, and the treated patients are getting injections of medication into the eye, so**

**the word "sham control" can actually mean different things in these studies. The perfect scientific sham control would be to inject the vehicle without the drug in the eye. Most doctors won't do it, most patients won't have it done, and most IRBs will not let you do it. So what is typically done instead is to do a sham injection, where you numb the eye of the patient, push on the outside with something blunt so you don't really inject medication. It's not a perfect scientific control because oftentimes the patients can tell if they were injected or not.**

Q. It's the accepted approach for an intervention like this?

**A. Yes. It's accepted because of the ethical issues associated with injecting saline into somebody's eye.**

Q. In this study, there were 63 clinical sites; correct?

MR. FELDSTEIN: Objection to form and foundation.

Q. If you look on page 577 under Methods, Study Design.

MR. FELDSTEIN: Same objections.

**A. This study mentions 63 sites, yes.**

Q. What is the reason for having multiple study sites instead of just one?

MR. FELDSTEIN: Objection to form and foundation.

**A. So there are several reasons. So the biggest reason is probably patient recruitment, because if you try to do this in two or three sites and you are looking for several hundred patients, this could take decades to enroll people.**

**The second reason is diversity of patient populations because in different geographies you are going to get different patient groups that are actually at risk for macular degeneration, so you don't want your study to have results which are limited to just one or two groups of people. You want a study which is a little more diverse than that. And those are probably the major two.**

Q. You would agree that one of the reasons for having multiple study sites in a clinical study is to have a representative sample of the study population?

MR. FELDSTEIN: Object to form.

**A. I think that's a reasonable statement, fair statement, yes.**

Q. And the third paragraph under Study

Design, two-thirds of the way through the paragraph, it references "independent reading center personnel" at the Duke Reading Center at Duke University.

Do you see that?

**A. Yes, I do.**

Q. Do you know what an independent reading center is?

**A. I do know what an independent reading center is, yes.**

Q. What is an independent reading center?

**A. So essentially for a very high quality study, you want the photographs to be read at an institution that's not actually treating the patients and never actually sees the patients. The ideal reading center would actually have photographs that are sent to it that are masked. And in a really good study, you wouldn't even know what sequence the pictures were taken in, so that prevents bias basically. It prevents somebody from saying oh, yeah, this drug appears to be working because they know that picture A actually came two years before picture B. So you can mask all that so the reading center personnel don't actually know that.**

Q. Take a look at the next page 578 under Geographic Atrophy Area Measurement and read that to yourself.

**A. Okay.**

**(Pause.)**

**A. Okay.**

Q. So you agree that in Exhibit 1066 that they masked the readers of an independent reading center, as you just described was the proper course on a high quality study; is that fair?

MR. FELDSTEIN: Object to form.

**A. So I do agree that their description is that their readers were masked at Duke.**

Q. And in fact, they had two experienced primary readers independently measure the geographic atrophy area at each time point; is that correct?

MR. FELDSTEIN: Object to form and foundation.

**A. Yes.**

Q. And what's the rationale for having two readers make the evaluation for each time point?

MR. FELDSTEIN: Objection to form and foundation.

**A. So drawing the area of geographic atrophy**

**and tracing of the software has some intrinsic error associated with it because you are looking at a picture and then trying to draw exactly where you think the normal retina stops and disease retina starts. So there is going to be some variation associated with that. It's pretty much standard in reading centers to have multiple graders read them and some reading centers use three, but it gets expensive every time you add a layer to this, so I think what they are doing, which is to have two, and then if there is more than a 10 percent discrepancy in the measurements, have the director of the reading center, Glenn Jaffe basically, you know, look at it and sort of adjudicate that number.**

Q. Now, the arbitration at the reading center, this is an independent reading center; correct?

MR. FELDSTEIN: Objection.

**A. The reading centers are independent, yes.**

Q. So in this study, the arbitration itself, not only was the original adjudication done by independent reviewers twice, the arbitrator who breaks the tie if there is one, is also an independent reviewer; is that correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. The arbitrator should be looking at this before the results of the trial are known. This particular person GJJ is the first author on this paper, but presumably when he was looking at the pictures did not know the result, and he himself probably or should not have actually even known when those photographs were taken and whether the patient was in a treated group or untreated group.**

Q. Would it have been appropriate to have an executive at the company sponsoring the trial be arbitrating or adjudicating the reading images instead of using an independent reading center?

MR. FELDSTEIN: Objection to form and foundation.

**A. In my opinion, that would not have been appropriate.**

Q. They give a lot of detail on this page about the software that they used for the reading and even the devices that they are reading, there is a lot of specific detail here.

Why do they give all of that detail here?

MR. FELDSTEIN: Objection to form and foundation.

**A. You are pointing to the Image Acquisition and Geographic Atrophy Area Measurement paragraph or something else?**

Q. Yes.

**A. So the equipment that is used to capture the image as well as how it's actually captured on the equipment has to be standardized because otherwise you'll get variation just because of that.**

**So these areas of atrophy, which are where there is really loss of cells, depending on the wavelength of the light, the color of light you are using to image that, you'll get a slightly different border, so you've got to make sure that it's done the same really in all of your centers and then analyzed the same when you get to the reading center. So the image acquisition part is really important, so that's why they talk about the number of stands and the type of unit that it was measured on, and they even specify on the Cirrus, which is a Zeiss product, that the OCT scans were measured in a certain way, 512 by 128 data points like on a screen.**

**And then the geographic atrophy measurement is done by a software called**

**RegionFinder, which is actually part of the instrument. And then the OCT, capital O, capital C, capital T, that's also standardized. So the more of these things you standardize, the less you are going to be prone to error, because if your measurement is not reproducible and your standard deviation is high, what's actually going to happen is if there is an effect there, you might completely miss it just because there's too much noise in the signal.**

Q. The next section says Study Endpoints; do you see that?

**A. Yes, I do.**

Q. So my question is: What was the prespecified primary efficacy endpoint of this trial?

MR. FELDSTEIN: Object to form and foundation.

**A. So their statement is as follows: The prespecified primary efficacy endpoint was the mean rate of change in GA area over 12 months measured by FAF, which is fundus autofluorescence, at three different time points: initially, at month 6, and month 12. So they actually looked at the area of geographic atrophy.**

Q. And in this study, was the prespecified primary efficacy endpoint satisfied?

MR. FELDSTEIN: Objection to form and foundation. Go ahead.

**A. I'm sorry, can you repeat the last word?**

Q. Satisfied.

**A. Satisfied?**

Q. Was it met?

MR. FELDSTEIN: Same objection.

**A. This is one of the earlier trials. I'd like to go back and look at their abstract again.**

Q. If it helps, on page 582, under Discussion, it says, "In this study," and then it gives the drug name, I won't try and say it, but it talks about it met its prespecified primary efficacy endpoint in reducing the mean geographic atrophy growth rate in participants with AMD.

Do you see that?

**A. Yes.**

Q. So you agree that in this study the study drug met its prespecified primary efficacy endpoint; correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. Yes, they did meet their endpoint.**

Q. And what is the significance of meeting the prespecified primary efficacy endpoint in this phase 2/3 trial?

**A. Well, it's important because the design of the trial, the Food and Drug Administration presumably already accepted that endpoint or they wouldn't have done the trial. So if you've gone into the study, designed it, had the FDA agree that this is the endpoint and then you go ahead and meet that endpoint, then the probability of FDA approval is quite high.**

Q. In this case, the study did result in FDA approval; correct?

MR. FELDSTEIN: Object to form, foundation.

**A. This drug was FDA approved. Whether there was another paper after this or not with longer time points, I don't recall, but this drug was FDA approved, yes.**

Q. Taking a look on page 577 of this document, the left-hand column, the bottom of the page, at this time point in 2021 when this was published, this says, Currently no FDA or European Medicines Agency-approved treatment is available for geographic atrophy.

**A. Can you point to which page you're on again?**

Q. 577, left-hand column, last paragraph.

**A. Yes. Starting in the middle of that sentence, "Currently no Food and Drug Administration or European Medicines Agency-approved treatment is available for GA." Correct.**

Q. And GA, geographic atrophy, is a subspecies of age-related macular degeneration; correct?

**A. It's -- yes, yes.**

Q. So before avacincaptad, there was no FDA-approved treatment for the geographic atrophy form of age-related macular degeneration; correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. There were two drugs that were approved at about the same time, and I don't recall which one was approved first. There was another complement which was also mentioned in my declaration called Syfovre and that received FDA approval at about the same time Zimura did, but I don't recall which one came first. They were separated by a few months.**

Q. If we take those two drugs, before them, there was no FDA-approved treatment for dry form of AMD; correct?

**A. For geographic atrophy, do you mean?**

Q. Let me back up and ask a different question. Geographic atrophy is an advanced form of dry AMD; correct?

**A. Yes, it is.**

Q. And before these two complement inhibitors were approved in 2023 there were no FDA approved treatments for geographic atrophy; correct?

**A. That is correct, yes.**

Q. And once they were approved, there were two FDA-approved treatments for geographic atrophy; correct?

**A. That is correct.**

Q. When were those two compounds created? When were they invented?

MR. FELDSTEIN: Object to form and foundation.

**A. I don't know the exact date that they were created. It was a few years before the studies. I don't know the exact date.**

Q. You don't know whether or not those two

compounds that were approved in 2023 were invented in 2005?

**A. The question is whether these two compounds were being investigated in 2005?**

Q. Whether they were invented in 2005.

MR. FELDSTEIN: Object to the form.

**A. I don't know, but I would doubt it. This was much later than the 2005 studies.**

Q. But so far as making the compounds themselves.

**A. I don't know when the compounds were actually made or manufactured, no.**

Q. So as part of doing your analysis in this case, you didn't investigate whether the two geographic atrophy therapies that have been approved by the FDA currently, whether they were invented, the compounds themselves, before September 2007; correct?

**A. I don't know whether these two compounds were invented before 2007.**

Q. Please take a look at page 582 of the exhibit. There is a heading that says Safety Analyses.

**A. Okay.**

Q. Do you see where it says that the study

drug was generally well tolerated?

**A. I do see that sentence, yes.**

Q. Do you see that it says that there were no reported ocular serious adverse events in the study eye?

**A. Yes, I do.**

Q. Please take a look at page 583 of the document.

**A. I'm at page 583.**

Q. In the left-hand column, the first paragraph, the second to the last sentence of the paragraph, do you see where it says, "The treatment effect was observed as early as month 6 and was maintained at month 12"?

**A. I see that sentence, yes.**

Q. So what does that mean?

MR. FELDSTEIN: Objection, form and foundation.

**A. Well, what the author is saying is that they observed the treatment effect at the 6-month time point and it continued, it was maintained to the 12-month time point.**

Q. So when it says it was observed, what does that mean that it was observed at 6 months?

MR. FELDSTEIN: Objection, form,

foundation.

**A. It means that when you look at the 6-month data that there is an observation that the treatment effect is there, but you're still continuing the study to 12 months.**

Q. When you say "an observation that treatment effect is there," does that mean there is a statistically significant difference between the study group as compared to the sham group?

MR. FELDSTEIN: Objection, form and foundation.

**A. So I can't tell that from that statement. I'd have to go back to the original data and see if the P value was significant in the 6-month time point.**

Q. Take a look at page 580 of the document.

**A. Okay.**

Q. Under Efficacy Endpoint Analysis.

**A. Okay.**

Q. The right-hand side gives you the P values at month 12.

Do you see that?

**A. I do, yes.**

Q. First of all, there is a 27.4 percent reduction in growth rate over 12 months in the 2

milligram treatment group as compared to sham; is that correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. Yes, that statement is -- that is what the statement reads.**

Q. And they have a P value of 0.0072.

Do you see that?

**A. The 12-month P value, I do see that, yes.**

Q. What is the significance of that particular P value?

MR. FELDSTEIN: Objection to form and foundation.

**A. So essentially a P value that low implies that the association seen was not likely to be by chance. Typically a P value is set at 0.05 or less, and if it is 0.05 or less, that's accepted for a reasonable P value in a clinical trial.**

Q. And if your prespecified endpoint is a P value of .05 or less, but you get a P value that's larger than .05, then you haven't met your primary endpoint; is that correct?

MR. FELDSTEIN: Objection to form.

**A. If the P value is less -- if you prespecified it, which most studies do, and you**

**don't meet .05, then you haven't met your primary endpoint.**

Q. What is the significance of failing to meet one's primary endpoint?

**A. Can you repeat the last part?**

Q. What's the implication or the significance of meeting -- failing to meet one's primary endpoint?

**A. Well, so if you don't meet your prespecified endpoint, there actually are two possibilities. So the first possibility is the drug doesn't work, which is by far the most likely. And the second possibility, which is very difficult to tease out, is that your study population wasn't large enough. So you might start thinking that if you wind up getting a P value of .06, for example, which means there is a 94 percent chance that the drug really does work, but it's not 95 percent, so it could mean either of those two things. But generally, it's regarded as a failure. Whether or not somebody would want to continue a study with that data is complicated.**

Q. Whether somebody wants to continue or not, that's up to them, but if they walked up to you and said, we did not meet our prespecified

primary endpoint, but we want you to call it a success, you'd be skeptical of that; right?

MR. FELDSTEIN: Objection to form. Incomplete hypothetical.

**A. That would be problematic, yes.**

**We might want to take another short break. Is this an okay time?**

Q. Yes, we can do that. We're between questions.

(Recess taken from 3:34 p.m. to 3:41 p.m.)

BY MR. MILLS:

Q. In the same exhibit, please look at page 583, left-hand column. At the bottom of the page, the very last paragraph, it starts with "Best-corrected visual acuity."

Do you see that?

**A. Yes, I do.**

Q. Is there an acronym for "best-corrected visual acuity" that you are familiar with?

**A. It's usually referred to as "BCVA."**

Q. And the reference says that BCVA is generally a poor indicator of functional vision in patients with geographic atrophy; correct?

**A. It does say that, yes.**

Q. And then it says, "The slow rate of

visual acuity loss over time precludes BCVA as an adequate primary efficacy endpoint in clinical trials for geographic atrophy."

Do you see that?

**A. Yes, I do.**

Q. On the right side of the page, the second to last paragraph, so the first -- the last full paragraph, it says that based on Food and Drug Administration guidance, best fit curve analyses showing a reduction in the rate of photoreceptor loss, reflected by reduction in geographic atrophy area growth rate between baseline and at least two subsequent time points with intervals of six months or more between them that exceeds measurement uncertainty is considered clinically meaningful.

Do you see that?

**A. Yes, I do.**

Q. So I want to make sure I understand that correctly. They are saying that if I have two time points that are at least six months apart and if there is a statistically significant difference between those and the baseline, the FDA says that that is clinically meaningful?

MR. FELDSTEIN: Object to form and foundation.

Q. Am I understanding what it says correctly?

MR. FELDSTEIN: Same objections.

**A. Let me read that paragraph again.**

**(Pause.)**

**A. Okay. Can you repeat the question?**

Q. So they are saying that if you have two time points that are at least six months apart and there is a statistically significant difference between each of those and the baseline, the FDA says that that is clinically meaningful; correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. So they are quoting another document, Reference 51, which I have not had a chance to review, but that is what they are saying, that Reference 51 says that, yes.**

Q. And it requires a difference that exceeds measurement uncertainty; correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. Yes, it has to exceed measurement uncertainty.**

Q. That's another way of saying that it needs to be a statistically significant result;

correct?

MR. FELDSTEIN: Objection to form and foundation.

**A. I think those are similar. I think those are similar statements. It means that it needs to exceed the error of the measurement or the measurement uncertainty by a certain amount, then typically that's considered to be two standard deviations.**

Q. And then they conclude on the basis of that FDA standard for clinical meaningfulness that the beneficial effects of avacincaptad pegol 2 milligrams or 4 milligrams to reduce geographic atrophy growth rate in this trial would be considered clinically meaningful; correct?

**A. So the authors of the study are coming to the conclusion that the beneficial effects of the drug to reduce GA growth rate of the trial would be considered clinically meaningful using the criteria they've quoted from Reference 51.**

Q. Thank you. You can set the document aside.

Let's take a look at -- I'm going to hand you what has been marked as Exhibit 1067 and I've got a copy for your lawyer.

MR. FELDSTEIN: Thank you. 1067?

MR. MILLS: Yes.

(Exhibit 1067, Lancet 2023 Article, Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials, Heier, et al., marked for identification.)

BY MR. MILLS:

Q. Do you recognize this document?

**A. Yes, I do.**

Q. What is it?

MR. FELDSTEIN: I'm sorry, I just want to preserve objections to the document for -- I want to make objections to Exhibit 1067 for authenticity, relevance and preserve other objections.

Q. So what is this document?

**A. It's a document on a clinical trial for a complement inhibitor for patients with macular degeneration.**

Q. So this is the second available therapy

for treating geographic atrophy that you referenced earlier; correct?

**A. Yes.**

Q. And I'm going to try and avoid pronouncing the active as much as I can, but I think we can save a lot of time on this one. I just want to kind of confirm there are some similarities to what they are doing in this study as compared to the other. So I guess one thing I want to ask is they used an independent reading center in this trial; correct?

MR. FELDSTEIN: Objection, form and foundation.

Q. And I'll direct you to page 1437 on the left-hand column, the first full paragraph, where it says, "The FAF images were evaluated in a central reading center by a minimum of two certified readers with independent manual measurements of features of the geographic atrophy lesions."

Do you see that?

**A. I do see that, yes.**

Q. So here they used a central reading center; correct?

MR. FELDSTEIN: Objection to form

and foundation.

**A. Yes, they state that they are using a central reading center.**

Q. Is that different than an independent reading center?

MR. FELDSTEIN: Objection to form and foundation.

**A. Is it different than --**

Q. An independent reading center.

MR. FELDSTEIN: Same objection.

**A. I don't know if they -- do they specify here? I don't see where they specify the reading center.**

Q. Would it make a difference to you if it were not an independent reading center?

MR. FELDSTEIN: Objection, form.

**A. Well, I don't think I'd want it to be part of the pharmaceutical company that's sponsoring the trial. I think that would make me uncomfortable, but I don't know where the reading center is.**

Q. It's referring to the readers as certified readers.

What does that mean to you?

**A. Certified readers usually means that the**

**readers have gone through a training portion of their reading and that they are certified as being self-consistent. By that I mean, you show them an image once, you show it to them again three days later, you show it to them again three days after that, that they are self-consistent, meaning that there is not too much variation in how they themselves are recording geographic atrophy. And then there is usually a reliability metric just like that between different readers. It's both intra and inter reader reliability. So most reading centers will certify their readers. They will say if this is over 90 percent, did they agree with themselves and agree with others.**

Q. I'm going to ask you in a moment whether the OAKS study satisfied its primary endpoint.

I'll direct you to page 1445. Under the Discussion section, the second full sentence where it says, "To our knowledge, OAKS is the first Phase III study of patients with geographic atrophy to meet its primary endpoint with a statistically significant growth difference in geographic atrophy lesions at 12 months in patients receiving this study drug monthly or every other month compared with sham."

Do you see that?

**A. The discussion paragraph starting about five lines down?**

Q. Yes.

**A. Yes, I do see that.**

Q. And then turning to the next page, on 1446, the left-hand column, the last full paragraph in the column, it starts with "Therapeutic Options."

**A. Yes.**

Q. Go ahead and read that paragraph to yourself, please, and then I'll ask you about it.

**A. Okay.**

Q. The second sentence says, "With the approval of pegcetacoplan by the FDA for the treatment of geographic atrophy secondary to AMD," and then it continues on to say, "a much needed therapeutic option has become available to patients."

Do you see that?

**A. It does say that, yes.**

Q. And I just want to make sure I understand when it's talking about a much needed therapeutic option that's become available to patients, it's referring to the pegcetacoplan that was approved by

the FDA; correct?

**A. Yes.**

MR. FELDSTEIN: Objection to form and foundation. Sorry, you've got to give me a minute.

Q. You can set that document aside.

**A. Apologies, yes.**

**(Exhibit 2171, previously marked.)**

Q. Do you have Exhibit 2171 in your binder?

**A. Yes, I do.**

Q. Okay. And this is one of the exhibits that you cited in your declaration; correct?

**A. Yes.**

Q. And this was published in what journal?

**A. This was published in either Ophthalmology or Ophthalmology Retina -- let me see if the reference is here -- which are two sister journals. Ophthalmology Retina.**

Q. Is that a reputable journal?

**A. Yes, it is.**

Q. And do you recognize the author of this paper?

**A. I do.**

Q. And he's a reputable fella I think; right?

**A. I think very highly of him, yeah.**

Q. In the left-hand column of this article, in the third sentence, it says, "Our own success, as two complement inhibitory drugs have been recently approved by the U.S. Food and Drug Administration, pegcetacoplan and avacincaptad pegol."

Do you see that?

**A. How far down the page are you?**

Q. The third sentence on the left-hand side.

**A. The third sentence on the left-hand side.**

Q. I'm on the first page of the article.

**A. The fifth line, yes, I do see that.**

Q. Okay. So those two drugs, those are the ones we've been discussing just now; correct?

**A. Yes, they are.**

Q. And so I just want to make sure I understand, when you say "our own success," the success is the pegcetacoplan and the avacincaptad pegol drugs that were approved by the FDA for the treatment of geographic atrophy secondary to dry AMD; correct?

**A. That is correct, yes.**

Q. In that same column, but further down, right before the next paragraph, so the second to

the last sentence, it says, "This progress has generated much excitement in the field, as evidenced by the recent acquisition of Iveric Bio by Astellas for the staggering sum of $5.9 billion."

Do you see that?

**A. I do.**

Q. So what you are referring to as progress that generated much excitement in the field, that's the FDA approval of those two drugs that we've been talking about; correct?

**A. Yes.**

Q. And that $5.9 billion that you call a staggering sum, why do you call it a staggering sum?

**A. It's one of the larger acquisitions of ophthalmic startups. It might be the largest actually, but it's a pretty large acquisition.**

Q. So from your perspective, is that a pretty large commercial success, to have an acquisition at that price?

MR. FELDSTEIN: Object to form, foundation.

**A. Well, I mean, I think it's a -- I think it's a -- I think it's a success to bring a product**

**to this point, you know, to FDA approval, and it's an acquisition by a larger company. This is an editorial, so it's sort of an opinion piece more than -- yes, but I think -- rephrase your question again.**

Q. So this is your opinion --

**A. Yes.**

MR. FELDSTEIN: Let him finish his question, doctor.

Q. The article accurately reflects your opinions; is that correct?

**A. Yes, it does.**

Q. On page 208, on the left-hand column, about two-thirds of the way down the paragraph, you talk about social media posts.

Do you see that?

**A. Yes, I do.**

Q. So you say there, "We are seeing posts on social media with physicians being proud to deliver intravitreal injections of complement inhibitors in patients with geographic atrophy."

Do you see that?

**A. I do see that, yes.**

Q. And then it says, "Finally, we have a drug to treat non-exudative age-related macular

degeneration."

Do you see that?

**A. Yes, I do.**

Q. And you finished that latter sentence with an exclamation point for emphasis; correct?

**A. I finished it with an exclamation point, yes.**

Q. And the exclamation point is for emphasis?

**A. I'm sorry?**

Q. The exclamation point is for emphasis?

**A. The exclamation point is to try and capture the exuberance of physicians posting on social media about the new availability of complement inhibitory drugs.**

Q. And that refers to the two FDA-approved drugs that we've been discussing today; right?

**A. Yes, it does.**

Q. Going back to page 207, on the right-hand column, towards the top of the page, starting about six lines down, it says, "Limiting progression of geographic atrophy is an important addition to our treatment armamentarium."

Do you see that?

**A. I do see that phrase.**

Q. So what is a treatment armamentarium?

**A. A treatment armamentarium refers to a potential portfolio of treatments as the field evolves.**

Q. So are you saying that the FDA-approved drugs for geographic atrophy are merely potential treatments for geographic atrophy, or are they existing treatments for geographic atrophy?

MR. FELDSTEIN: Object to form.

**A. Can you repeat the question for me?**

Q. Are you saying that the FDA-approved treatments for geographic atrophy are merely potential treatments or are they existing treatments?

MR. FELDSTEIN: Object to form.

**A. So at the time this editorial was written, they were existing treatments for geographic atrophy.**

Q. And at the time this editorial was written, they were the only treatments for geographic atrophy; correct?

**A. Yes. That's correct.**

Q. Before I hand you another document, I want to go back to your experience.

So you yourself have actually

participated in creating treatment for -- to be administered to Stargardt patients; is that correct?

**A. I'm not sure which studies you are referring to. I was involved in some of the earlier studies on stem cell therapy for Stargardt disease, so if that's what you are referring to, the answer is yes.**

Q. Are there any other studies that you've done for treating Stargardt patients?

**A. We've done natural history studies on Stargardt, but for treatment, it would be the stem cell study.**

Q. And in the stem cell studies, at least in one of those studies, you had 18 patients and 17 of them got better or stayed the same and only one got worse; is that correct?

**A. I'd have to go back and look at the original study to refresh my memory. The original publication in Lancet had -- in the original study that was published in the journal Lancet, there were two groups of patients that were treated, one group had Stargardt disease with essential atrophy from that. And then a second group of patients actually had dry macular degeneration with**

**geographic atrophy.**

Q. And in either of those sub-groups, did you see patients who received the stem cell treatment show positive results?

**A. So it was a safety study, not an efficacy study, but there was a difference in visual acuity at the latest time point that was statistically significant in the geographic atrophy group from macular degeneration, and that looked promising in the Stargardt but the P value was slightly greater than .05.**

Q. When were those results published?

**A. So that paper was published around 2015 or 2016.**

**(Exhibit 1068, 2019 American Academy of Ophthalmology Article, Natural History of Autosomal Recessive Stargardt Disease in Untreated Eyes, A Systemic Review and Meta-analysis of Study and Individual-Level Data, Shen, et al., marked for identification.)**

BY MR. MILLS:

Q. I'm handing you Exhibit 1068.

MR. FELDSTEIN: I object to Exhibit

1068 on relevance and foundation and reserve other objections.

Q. Do you recognize Exhibit 1068?

**A. Yes, I do.**

Q. This is an article, we could call it Shen, from 2009 in the Journal of Ophthalmology; correct?

MR. FELDSTEIN: You misspoke, counsel, the year.

Q. Let me start over. This is an article by Shen from 2019 in the Journal of Ophthalmology; correct?

**A. Yes.**

Q. And you are one of the coauthors on this paper?

**A. Yes, I am.**

Q. And you recognize this as the document that was published in 2019 in Ophthalmology?

**A. Yes, I do.**

Q. This was a peer-reviewed publication?

**A. Yes.**

Q. And the Journal of Ophthalmology is a reputable journal in the field?

**A. Yes, it is.**

Q. Please take a look at page 1294 of the

document.

**A. Okay.**

Q. Left-hand column, the end of the first paragraph, there is a sentence that starts "This suggests." Actually, why don't you go ahead and read to yourself that entire paragraph. It starts on the prior page and continues on.

**A. The paragraph that ends with "This suggests that although atrophy"?**

Q. Yes.

(Pause.)

**A. Okay.**

Q. So that paragraph, the gist of that paragraph is that, I think it's summarized in the last sentence there, that atrophy and geographic atrophy starts at a much later age than Stargardt 1. The rate of RPE cell loss resulting from geographic atrophy is much faster than that of Stargardt 1 after the atrophy has begun; is that correct?

**A. Yes, that is correct.**

Q. Stargardt 1, STGD 1 there, what does that refer to?

**A. It refers to Stargardt's disease associated with the ABCA4 mutation. So Stargardt's**

**disease was named by Stargardt, like Nancy Nadi (phonetic), based on what the patient looked like, and that classification, called a morphological classification, what do you see and what do you think the disease is, sort of still stays with us.**

**So there are patients with Stargardt's who have different gene mutations, but most patients have this ABCA4 mutation, and that's been sublabeled Stargardt 1.**

Q. And in particular, is it true that the Stargardt 1 is individuals that have a double mutation in that gene?

**A. It is a recessive disease, so you have to have both genes.**

Q. So you mentioned there is multiple different types of Stargardt disease. In this case, you have some discussion about the TEASE, T-E-A-S-E, trials.

Do you know what I'm talking about?

**A. I do recall that, yes.**

Q. And in particular, I think you testified about TEASE 1 and TEASE 3.

Does that sound correct to you?

**A. Yes, it does.**

Q. And you haven't offered any testimony

about TEASE 2 or TEASE 4, correct?

MR. FELDSTEIN: Object to form.

**A. My declaration contains information on TEASE 1 and TEASE 3, yes.**

Q. TEASE 1 and TEASE 3 both were limited to Stargardt patients; correct?

**A. TEASE 1 and TEASE 3 are limited to patients with the ABCA4 mutation which would be categorized as Stargardt 1.**

Q. And in this reference, Exhibit 1068 that we're talking about here, they are telling us that geographic atrophy resulting from age-related macular degeneration takes longer to happen. But once it happens, it happens much faster than in the Stargardt disease; correct?

**A. Once it happens, the cell loss is happening faster than Stargardt's.**

Q. Please look -- take a look on the right-hand side, the right-hand column now, near the bottom of the page, right above the link that says aaojournal.org, it says, "BCVA does not seem to correlate with atrophic lesion sizes."

Do you see that?

**A. Yes, I do see that.**

Q. On the basis of that lack of correlation

in your article here in 2019, you concluded that BCVA may not be a reliable measure to monitor Stargardt 1 progression.

Do you see that?

**A. Yes, I do.**

Q. Take a look at the abstract at the beginning of the paper. Under Methods, the study is evaluating several different ways to make sense of the data they are seeing; is that right?

**A. Can you repeat that statement?**

Q. Let me ask a different question. Let me see if I can be more clear. The fourth line under Methods, it says, "Radius linear model, RLM."

Do you see that?

**A. I do.**

Q. So this paper ultimately concludes that radius linear model is the appropriate or best way to measure the reduction and progression of the atrophy; is that correct?

**A. Yes, that is correct.**

Q. Okay. On the right-hand side of that page, so out of the abstract, right-hand side of the column, it says that the different studies using FAF have reported mean growth rates for atrophic lesions that vary widely from 0.39 to 1.84

millimeter square per year.

Do you see that?

**A. I see that sentence, yes.**

Q. So what was the significance in your article here of the wide variation that you found in studies that had used FAF to try and measure growth rates of atrophic lesions?

**A. Can you repeat that again?**

Q. So why are you all talking about that wide variation in growth rate here? What was the significance of it to you?

**A. Well, so the reason it's important is that to look at potential treatments, it's important to know what the natural history of disease is, and what we were observing in this is that when you went back and looked at the prior studies on Stargardt, that the growth rates reported just varied extensively all over the place by a factor of almost 5, you know, from one study to another.**

**So the question is: Why do you have this kind of variation? And our hypothesis was that there is more uniformity than you think, but because patients are coming into the study at different time points in the disease, that if you**

**adjust for that you'll get rid a lot of this variation and just be able to determine the growth rate.**

Q. If I understand you correctly, you're saying when we're measuring -- we are trying to measure whether we've slowed the progression, we kind of need a baseline to say, well, where would it have gone if we hadn't treated?

**A. Yes. You need good baseline data and you need to be able to design your study so you can detect differences.**

Q. And I think you referred to that as "natural history"?

**A. "Natural history" basically means what occurs if you don't intervene at all.**

Q. I want to ask you a question about the TEASE 3 trial; do you recall that trial?

**A. I do.**

Q. And that trial is a very small sample size of siblings; is that correct?

**A. Yes.**

Q. Do you recall approximately how many individuals were involved in this study?

**A. The original report was three, three patients and with each of them having an older**

**sibling.**

Q. Okay. And basically what they were trying to do is use the older sibling as kind of the natural history for the younger sibling and say, well, let's assume that at 24, you know, the older sibling had, you know, this much atrophy and so if you have less atrophy at 24 than big brother did, then we are going to think that maybe there was a slowing of progression.

Is that at a high level a description of what's attempted in that trial?

MR. FELDSTEIN: Object to form.

**A. So I think they were looking at two things. So the first one is, you are not 24 yet, but you are going to be 24 in a couple of years so then it's exactly what you just said.**

**But then the second thing they looked at was sort of progression from where you are, and they compared the progression rate in the older siblings to the progression rate in the younger siblings. So they were separated by just a few years.**

**Anyway, that's what I think they were trying to do.**

Q. So it was a two-year difference, right,

between the siblings, each sibling set?

**A. I don't remember the exact ages, but that was approximately it, yes.**

Q. So now I have a question about existing Stargardt advice. So do you actually treat patients who have Stargardt?

**A. I see patients with Stargardt disease, yes.**

Q. In the 2015 time frame, what would you tell your Stargardt patients when you diagnose them with Stargardt disease, what would you tell them to do?

**A. So I would -- my typical evaluation of Stargardt patients is at the beginning to look at them clinically, talk to them about Stargardt -- a lot of patients already have the diagnosis, they've been walking around with it, but some of them were new patients that were completely unaware -- to send them for genetic testing to ensure that that was indeed the mutation they had.**

**On a separate visit, they would see me. I would tell them what I thought they had, do the appropriate tests, send them for gene testing, and then usually the follow-up visit was with one of our other physicians who pretty much does**

**exclusively retinal degeneration work. And I might talk to them very generally about clinical trials, but usually that conversation was left for the second doctor that saw them after we had the gene therapy results -- the gene identification results.**

Q. Do you have a sense for what advice your colleague would be giving to those patients once they are diagnosed with Stargardt disease in 2015?

**A. I don't actually know what this individual physician would say for each patient, but a very logical management of patients in that time frame was to refer them to one of these clinical trials that Alkeus was doing.**

Q. And specifically Alkeus or clinical trials in general?

**A. So this usually happened after I had initially evaluated the patient, but a logical sequence of events was once you had the gene defect to go to a website, clinicaltrials.gov, look and see every clinical trial the patient might be eligible for, including some of the stem cell studies for patients who had severe advanced disease with already lost vision, and those patients just stopped in the progression might not be something that would make anybody happy, neither**

**the doctor or the patient, and then talking to the patients about the clinical trial options.**

Q. Are there any lifestyle modifications that would have been offered to the patient as advice to attempt to ameliorate the Stargardt syndrome?

**A. That would have happened after I saw them. I would not usually talk to patients about that because I always refer them to another retinal specialist afterwards.**

Q. So you don't know what lifestyle modifications might have been offered?

**A. There is literature on light, you know, that minimizing light, but that's a tough one because the last thing you want to do for a patient that's already having trouble seeing is to ask them to turn the lights down. Their vision might last longer, but they are going to have more trouble seeing.**

Q. In your view, making it more difficult for a Stargardt patient to see would not be a recommended treatment option?

MR. FELDSTEIN: Objection to form.

**A. It would be worth discussing, but it would come with certain caveats.**

Q. Let's set that document aside. I have a question about -- so the clinical studies, we talked about TEASE 1 and TEASE 3. You have a third study that you've discussed in your declaration, that's the SAGA trial; correct?

**A. That is correct, yes.**

Q. And the SAGA trial is for geographic atrophy?

**A. It's for geographic atrophy, for macular degeneration, yes.**

Q. You are aware that the SAGA trial failed to meet its primary endpoint; correct?

**A. The SAGA trial had some data initially that suggested a potential treatment benefit, and their final endpoint, I don't know where it went after that, but I'm aware of the SAGA trial results, yes.**

Q. And are you offering an opinion in this case that the SAGA trial results satisfied their prespecified primary endpoint?

**A. No, I'm not offering that opinion.**

Q. And as far as you're aware, it's correct that the SAGA trial did not meet its prespecified primary endpoint; correct?

**A. My recollection of the SAGA trial is they**

**saw in the first cohort of patients a small treatment benefit that was -- may have not been borne out subsequently.**

Q. And as a result of that, the SAGA trial was unable to report that they met the prespecified primary endpoint; correct?

**A. Yes, that's correct.**

Q. What was actually administered to the patients in the SAGA trial?

**A. ALK-001. I don't recall if the SAGA trial had one dose or two doses of it. The 14 milligram was one of the doses. One of the trials, TEASE, I believe had a higher dose, but I'd have to go back and look at that.**

Q. And other than -- well, first of all, ALK-001, is that a specific compound?

**A. Yes.**

Q. And what compound is that?

**A. C20 deuterated form of vitamin A.**

Q. And in particular, it's a trideuterated, it's C20 trideuterated form of vitamin A; correct?

**A. Yes. There are three deuteriums at that position.**

Q. So for all of the gildeuretinol trials that you discuss, none of them have any study of a

monodeuterated version of vitamin A; correct?

**A. The three trials that we are talking about all gave the trideuterated version, yes.**

Q. And in particular, it was a specific form of vitamin A that was -- it was a C20 trideuterated retinyl acetate; correct?

**A. Yes.**

Q. And are there other names that are used that are for retinyl acetate that mean the exact same thing, other chemical names that equate to that?

**A. Well, I mean, there is a drug name gildeuretinol. Is that what you are referring to?**

Q. I want to get all the synonyms on the table just so that there is no ambiguity.

**A. The drug is a sub-class, is a sub-type of retinol ester, retinyl ester, which is also retinol ester. There is a variety of names that are used for it. I'd have to go back to my declaration to be complete about that list, which I'm happy to do.**

Q. What I'd like to do -- so first of all, all of the studies of gildeuretinol that you discuss in your declaration, all of them are administering the exact same compound; correct?

**A. That is my understanding, yes.**

Q. And it's this retinyl acetate C20 trideuterated compound; correct?

**A. Yes.**

Q. What was the formulation into which the C20 trideuterated retinyl acetate was placed in the three studies?

**A. I'd have to go back to the exhibit to look at that quickly.**

**I best find it by going here and then seeing the exhibit number.**

Q. If you want to tell me what you are looking for, I can see if I can find the number for you.

**A. Actually, just the TEASE and SAGA, but that might not have it. The exhibit numbers for the press releases related to the TEASE trial and the SAGA trial is what I'm looking for which may or may not have that information within them.**

Q. So they start at 2097. And while you are looking, really my question is: Is there a different formulation used in each one, or is it always the exact same thing that's actually being administered?

**A. So just to clarify, are you speaking about the active molecule or about the excipient or**

**delivery vehicle that it's in?**

Q. I want to know -- let me ask a predicate question: This is administered orally in a capsule in all three trials; correct?

**A. It's administered orally, yes.**

Q. So are there any differences between what was administered in one trial versus the others?

**A. I am not aware of any differences between them. I think they are the same thing.**

Q. Okay. So I guess what I'm asking is: Is there something special about the formulation, the excipients that it's put in that make it work differently than the compound itself?

**A. So the functional part of the molecule is the same in all three trials. The excipients can be very important for absorption across the gut, the kinetics, you know, how long the molecule is in the gut for, so they can certainly have an effect, but I don't have enough knowledge on these to be able to comment on that.**

Q. You used the phrasing the functional portion of the molecule. I think what you really meant is the active ingredient molecule is the same between all three; is that what you meant?

**A. That is what I meant, yes.**

Q. So you are saying that in some cases the formulation that's used could be responsible for the effect that you're getting when you administer the drug?

MR. FELDSTEIN: Objection. Misstates the testimony.

**A. I'm saying the formulation that's used is important because it can control -- it can affect a lot of variables, including just absorption of a medication that's swallowed.**

Q. Okay. And you don't know what the formulation is that was used to administer ALK-001 in the trials that you relied on; is that correct?

**A. Well, I think it's described as a soft gelatin capsule, but aside from that, I can't tell you exactly what was in it, no.**

Q. And did you review the patent that's at issue in this case?

**A. The '045 patent?**

Q. Yes.

**A. Yes.**

Q. Does that patent tell us anywhere in the claims the formulation for administering the active ingredient?

MR. FELDSTEIN: Object to form.

**A. So there are parts of the patent that refer to a pharmaceutically acceptable carrier, for example, claim 29.**

Q. But it's not a specific pharmaceutically acceptable carrier; right?

**A. So on column 17, for example, there is a broad range. "Solid dosage forms for oral administration. Capsules, tablets, pills, powders, granules and the like may be prepared by mixing the active ingredient with one or more pharmaceutically acceptable carriers and, optionally, one or more fillers," and then it sort of goes on for a dozen lines.**

Q. It's pretty open about what can be used; right?

**A. I mean the same thing in column 16. The entire column is basically devoted to different things that can be in it.**

Q. In the claims, the claims at the end of the patent, it doesn't tell us -- none of the claims specify a particular pharmaceutical formulation; is that correct?

**A. I don't recall a specific pharmaceutical carrier, but I really have to read the claims carefully to agree with that statement, one by one.**

Q. In your review of the claims just now, is there any claim that specifies oral administration?

**A. So can you repeat the question?**

Q. Do any of the claims require oral administration?

**A. While I prefer to answer that by doing a careful search for the word "oral" or "parenteral," something like that, but I'm not seeing it on the claims standing now in front of me.**

**(Exhibit 1006, previously marked.)**

Q. Can you open to Exhibit 1006.

**A. Okay.**

Q. Do you recognize this document?

**A. Yes, I do.**

Q. What is this document?

**A. It's paper written by Bergen, Furr and Olson.**

Q. And what's the -- there is an asterisk above the name of James A. Olson; what does that asterisk represent?

MR. FELDSTEIN: Object to form, foundation.

**A. It basically is telling you who you should direct correspondence to about the article.**

Q. So is Olson a grad student or the person

that runs the lab?

MR. FELDSTEIN: Objection to form, foundation.

**A. Well, they could really be either, but typically it's the person who runs the lab.**

Q. Let's take a look at page, it says 12, but it's the second page in the document. Up at the top, there is a diagram with a numbering system for retinol.

Do you see that?

**A. Yes, I do.**

Q. And do you see carbon 20 on there?

**A. Yes.**

Q. Is that, as you understand it, the same numbering system that is used in the claims of the patent when they refer to a C20 deuterated retinoid?

**A. I believe that is the same numbering system.**

Q. Under the Discussion, the third line, it says -- they are talking about a route for synthesis of 20,20,20-trideuteroretinol.

Do you see that?

**A. "The advantages of this route for synthesis of 20,20,20-trideuteroretinol." I do see**

**that, yes.**

Q. So I just want to make sure. That's the same compound in the claims of the patent when they talk about that the C20-D1-3-retinoid is selected from the group consisting of C20-D1-3-retinol. That's the same compound; correct?

MR. FELDSTEIN: Object to form. Foundation.

**A. So the deuteration is at carbon 20, the tail on the right-hand side can vary, but the deuteration is a carbon 20, yes.**

Q. And what you are saying is in the claim, the tail can vary; it can be an alcohol, an aldehyde or an ester. Here in the Olson reference from 1988, the example I pointed to on page 12 is the alcohol version of the claimed compound; correct?

**A. That's the alcohol version, correct.**

Q. The alcohol version of the claimed compound; correct?

**A. Yes.**

Q. And then if we look on page 13, where they have a synthesis scheme, they have retinol number 7, and they have retinyl acetate number 8.

Do you see that?

**A. I do see that, yes.**

Q. And it says, Scheme 2, Synthesis of deuterated forms of vitamin A.

Do you see that?

**A. Yes.**

Q. And then it says 20,20,20-2 -- a little 2 that's up high, and then an H, and then a 3 that's down below, and that says retinoic acid ethyl ester.

Do you see that?

**A. Yes, I do see that.**

Q. So the 20,20,20-2H3, that means C20 trideuterated; do you agree?

**A. I believe that's what they are referring to, yes.**

Q. And then it says, retinoic acid ethyl ester and the R1 group is a CH3.

Do you see that?

**A. I do.**

Q. And the R4 group is a C2H3; correct?

**A. I see that, that printed line, the third line down.**

Q. So that means that the R4 group is a trideuterated carbon; correct?

**A. Yes.**

Q. And in the scheme, the retinyl acetate compound 8, the R4 is the carbon 20; correct?

**A. Can you repeat that again?**

Q. So on page 13 of Exhibit 1006, the R4 in the retinyl acetate compound that's labeled number 8, that's the carbon 20; correct?

**A. Yes, that's correct.**

Q. On this page, what they are depicting is that this is a C20 trideuterated retinyl acetate compound; correct?

**A. This page is depicting trideuteration of the carbon 20 position.**

Q. Of retinyl acetate; correct?

**A. So the retinyl acetate is shown on the lower right, it's labeled with the number 8, and I don't see which molecule specifically they are referring to in lines 3 and 4. It looks like they -- there's two lines that say retinyl acetate, essentially the fourth line in the scheme legend and the fifth line both say retinyl acetate.**

Q. We're looking at the scheme itself, the very last compound number 8, the retinyl acetate.

**A. I can see the compound scheme, yes.**

Q. And where it has the R4, do you see that?

**A. I see R4 in several places.**

Q. Okay. And in each of those places, the R4 is deuterated; correct?

MR. FELDSTEIN: Object to form.

**A. So in the last line, 4, very last line, it says R4-CH3. And the deuteration is R2 and it has 1 deuterium at R2.**

Q. Yes, thank you. Okay.

So other than the fourth line, the 10,19,19,19, the middle three lines all have deuteration at carbon 20; correct?

**A. The middle three lines have deuteration at carbon 20, correct.**

Q. And if we're looking at the first line compound, the one that says 20,20,20-2H3-retinoic acid ethyl ester, that one is trideuterated at carbon 20; correct?

**A. That is trideuterated at carbon 20. That's line 2, yes.**

Q. So that is C20 trideuterated retinyl acetate; do you agree?

MR. FELDSTEIN: Object to form. Misstates the reference.

**A. What's referred to in line 2 is a trideuterated retinoic acid ester.**

Q. And that particular retinoic acid ethyl

ester is what you get when R1 is a CH3 and R4 is trideuterated; correct?

MR. FELDSTEIN: Object to form.

**A. Well, the R4 is definitely trideuterated, and the R1 here is just a CH3 group.**

Q. Right. So you agree that that line is referring to C20 trideuterated retinyl acetate; correct?

MR. FELDSTEIN: Object. Object to form. Misstates the reference.

**A. I don't think I agree with that. It looks -- I can't tell which line -- I can't tell which stick figure is being referred to in line 2 from the way this is written.**

Q. So you understand this is a synthesis scheme; correct?

**A. Yes, I do.**

Q. And the ultimate outcome of the synthesis scheme is retinyl acetate; correct?

MR. FELDSTEIN: Objection. Form, foundation, misstates the document.

**A. I understand this is a synthesis scheme. And I understand they are trying to make deuterated forms of vitamin A that have 3, 4 or 5 deuteriums on them.**

Q. The very last step of the synthesis is taking the retinol and making it into retinyl acetate; correct?

MR. FELDSTEIN: Objection.

**A. So for clarification, there are eight stick figures, so I'm not sure which one you are referring to.**

Q. So referring to the compound labeled 7 and the compound labeled 8.

**A. Okay, I see those two.**

Q. So in the step going from 7 to 8, they are going from a retinol to a retinyl acetate; correct?

**A. Between 7 and 8, you are going from retinol to retinyl acetate, correct.**

Q. And in each of those figures, there is the very same R1 and R4 labeling; correct?

MR. FELDSTEIN: Objection to form. Foundation, misstates the reference.

**A. So each of those stick figures shows R1 and R4 in the same position, yes.**

Q. And when there is synthesis of C20 trideuterated retinoic acid ethyl ester, the R4 is trideuterated; correct?

**A. Line 2, the retinoic acid ethyl ester has**

**three deuteriums at R4; correct.**

Q. So Dr. Del Priore, can you look up at me now?

**A. Yes.**

Q. Are you disputing that the Olson 1988 reference discloses C20 trideuterated retinyl acetate?

MR. FELDSTEIN: Objection to form. Asked and answered.

**A. I'm trying to correlate what's in the text to what's in the figure because this is actually particularly confusing the way they've done this.**

Q. Okay. Let's take a look at page 15 of the reference.

**A. Okay.**

Q. There is a heading that says Experimental.

**A. Same reference, I assume.**

Q. Yes.

**A. Okay, I see that.**

Q. Under Experimental, it says, "Synthesis of 20,20,20-trideuteroretinyl acetate."

Do you see that?

**A. I do.**

Q. So, Dr. Del Priore, are you disputing that the Olson 1988 reference discloses making C20 trideuterated retinyl acetate?

MR. FELDSTEIN: Objection to form, foundation, beyond the scope.

**A. I think in their methods, they are trying to synthesize exactly what you just said, the trideuterated form, yes.**

Q. Please take a look at page 18 of the document.

**A. Okay.**

Q. The third paragraph, it starts with C20 trideuterated retinol compound 7; correct?

**A. The third paragraph says 20,20,20-2H3, which is deuterium retinol, it then has a 7 next to it, yes.**

Q. And it says there's one gram; correct?

**A. It says -- can you repeat that?**

Q. It says there's one gram?

MR. FELDSTEIN: Sorry, where are you looking?

Q. It says 1 gram, .003 mols.

**A. Yes, I see that.**

Q. So the starting point in that paragraph is C20 trideuterated retinol; correct?

**A. Yes.**

Q. And you agree that that's the same C20 trideuterated retinol that's recited in the claims of the challenged patent; correct?

**A. Yes.**

Q. At the end of that paragraph, it says that the product of the reaction is C20 trideuterated retinyl acetate which it refers to as compound 8.

Do you see that?

**A. I do not see that at the end of that paragraph. Mine says, "The isomers were separated." Is it above that?**

Q. It's right immediately before that.

**A. I'm probably just looking at the wrong place. The sentence before that says, "The organic layer was dried and rotory-evaporated to give an overall crude yield of 60 percent."**

Q. Yes, 60 percent, 20,20,20-2H3-retinyl acetate 8.

Do you see it?

**A. Yes, I do.**

Q. So you agree that the product of the reaction in this paragraph that started with C20 trideuterated retinol compound 7 was C20

trideuterated retinyl acetate compound 8; correct?

**A. Yes, it does say that.**

Q. And that is the same compound that, for instance, claim 8 of the challenged patent recites; correct?

**A. I'd like to look at paragraph 8 and compare it.**

Q. Please go ahead. But it's claim 8, claim 8.

**A. Claim 8.**

**(Pause.)**

**A. Okay. Can you repeat the question for me?**

Q. So you agree that the C20 trideuterated retinol acetate in the Olson 1988 reference is the same compound that's claimed by the '045 patent, correct?

MR. FELDSTEIN: Objection to form.

**A. They appear to be referring to the same compound, yes.**

Q. And you agree that the Olson 1988 reference has a publication year of 1988?

MR. FELDSTEIN: Objection, form and foundation.

**A. So that reference was published in 1987,**

**the Olson reference, yes.**

Q. And you agree that as of -- before September 2007, the Olson 1988 reference, Exhibit 1006, had already disclosed in the prior art the C20 trideuterated retinol acetate that's claimed in the '045 patent; correct?

MR. FELDSTEIN: Objection, form and foundation.

**A. I agree that the 1987 paper discloses that molecule.**

Q. You agree that in 2007, in September 2007 that that molecule was not a novel molecule; correct?

MR. FELDSTEIN: Objection to form, foundation, legal conclusion. Beyond the scope.

**A. I agree that that molecule was disclosed in the 1987 publication that we are referring to.**

Q. Now, Dr. Del Priore, you can put the document down and just look at me for a minute.

**A. Okay.**

Q. Are you aware that Alkeus has been pitching to its investors and potential investors to give them money by telling them that they have a novel compound?

MR. FELDSTEIN: Objection to form

and foundation. Beyond the scope.

**A. I don't have any knowledge of that one way or another.**

Q. So you agree that if anyone is calling C20 trideuterated retinol acetate a novel compound that they are mistaken?

MR. FELDSTEIN: Objection to form, foundation and beyond the scope.

THE WITNESS: I should answer?

MR. FELDSTEIN: If you can answer.

THE WITNESS: I'm sorry, can you repeat that?

MR. FELDSTEIN: If you can answer.

**A. Can you ask the question again?**

Q. You agree that if anyone is calling C20 trideuterated retinol acetate a novel compound, they are mistaken?

MR. FELDSTEIN: Objection to form, foundation, beyond the scope, incomplete hypothetical.

**A. I agree that that molecule with three deuteriums is referenced in the 1987 paper.**

Q. Now, you seem to me to be a very honest person.

**A. Yes.**

Q. You've been very forthright today. Am I correct in assuming that going forward if somebody asked you whether C20 trideuterated retinol acetate is a novel compound that you would say it's not, it was disclosed in the prior art in 1988?

MR. FELDSTEIN: Objection to form, foundation, beyond the scope, incomplete hypothetical.

**A. I'm feeling uncomfortable with the organic chemistry part because there could be minor differences in molecules that can have important functional differences. The stick figures in these papers, they are confusing the way they are labeled, so I'd like -- I would like to review that in further detail and look at this in more detail before I answer that definitively. I can't tell if they are identical or not. I can tell that it's deuterium at that position but...**

Q. Dr. Del Priore, before working on this case, had you had any interactions at all with Alkeus?

**A. No.**

Q. Had you had any interactions at all with the attorneys that you worked with on this case?

**A. Prior to this case?**

Q. Right.

**A. No, I did not.**

MR. MILLS: Can we go off the record.

MR. FELDSTEIN: Okay.

(Recess taken from 4:52 p.m. to 4:58 p.m.)

BY MR. MILLS:

Q. Dr. Del Priore, did you review in this case the Prestwich declaration?

**A. I'm not sure. Mention the name of it again.**

Q. Prestwich.

**A. That's the author's name? I'd have to look at it by exhibit number.**

Q. You can check and see, I think it's 2195. See if you have that one there.

**A. Okay.**

Q. Not 2195.

**A. I go to 2193 and then it stops.**

Q. It's actually 2052.

Let me ask you this question: Do you know who Dr. Prestwich is?

**A. Not by name, no.**

Q. Did you speak with any Alkeus personnel in preparation for your declaration or for this

deposition?

MR. FELDSTEIN: I think he's moved on to a different question, doctor. You don't have to look for the document.

**A. Which personnel are you referring to?**

Q. Anyone at Alkeus.

**A. No, no.**

Q. Anyone at the owner of the patent?

**A. No.**

Q. Did you speak with Ilyas Washington at any point in this case?

**A. I didn't.**

Q. What about Dr. Saad, S-a-a-d?

**A. I've not spoken with him, no.**

Q. What about Dr. Kim at Alkeus?

**A. No.**

Q. Have you spoken with any of the authors of any of the references, except for yourself, that you've relied on in your declaration --

MR. FELDSTEIN: Object --

Q. -- about this case?

**A. No. Not about this case, no.**

Q. Did you review the institution decision in this case?

**A. Did I review the institutional --**

Q. Institution decision in this case.

MR. FELDSTEIN: Object to form and foundation.

**A. Okay. Which exhibit is the institution?**

Q. It wouldn't be an exhibit. It would be basically an order from the board.

**A. No, I don't recall reviewing that.**

Q. Are you aware that there was a second case that -- actually, I'm going to withdraw that question.

**A. Okay.**

MR. MILLS: And I'm going to thank you for your time.

MR. FELDSTEIN: Okay. We are off the record.

MR. MILLS: Yes.

(Recess taken from 5:01 p.m. to 5:05 p.m.)

MR. FELDSTEIN: No further questions.

Thank you, doctor, for your time. Off the record.

(Time Noted: 5:05 p.m.)

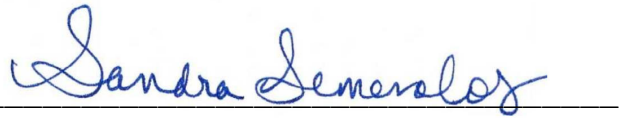
CERTIFICATE OF REPORTER

I, SANDRA SEMEVOLOS, a Registered Merit Reporter and Notary Public within and for the State of Connecticut, the officer before whom proceedings were taken, do hereby certify that the foregoing transcript is a true and accurate record of these proceedings; that said proceedings were taken in Stenotype by me on the 13th day of November 2024, commencing at 9:06 a.m. and ending at 5:05 p.m.

I further certify that present on behalf of Party Gene Company Pty Ltd., Jad A. Mills, Esq., of Wilson Sonsini Goodrich & Rosati, P.C., and on behalf of Party The Trustees of Columbia University in the City of New York were Mark J. Feldstein, Esq., and William C. Neer, Esq., of Finnegan, Henderson, Farabow, Garrett & Dunner, LLP.

I further certify that I am not related to, nor associated with any of the parties or their attorneys, nor do I have any disqualifying interest, personal or financial in this action.

Dated: 25th day of November, 2024, at Hartford, CT.



Sandra Semevolos, RMR, CRR, CSR #74

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