UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ALVOTECH USA INC. and ALVOTECH HF,

Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,

Patent Owner.

Case: PGR2025-00085

U.S. Patent No. 12,168,036

- - -

DEPOSITION OF

DONALD J. D'AMICO, M.D.

Fish & Richardson

7 Times Square

New York, New York

9:00 a.m. EST

June 2, 2026

REPORTED BY: MARIE FOLEY, RMR CRR

DIGITAL EVIDENCE GROUP

1730 M Street, NW, Suite 812

Washington, D.C. 20036

(202) 232-0646

VIDEOTAPED DEPOSITION of DONALD J. D'AMICO, M.D., conducted at Fish & Richardson, 7 Times Square, New York, New York, commencing at 9:00 a.m. EST, on the above date, before Marie Foley, a Registered Merit Reporter, Certified Realtime Reporter and Notary Public.

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APPEARANCES:

ON BEHALF OF PETITIONER:
FISH & RICHARDSON P.C.
BY: MEGAN CHACON, ESQUIRE
12860 El Camino Real
Suite 400
San Diego, California 92130
PHONE: 858.678.5070
EMAIL: chacon@fr.com

ON BEHALF OF RESPONDENT:
WILLIAMS & CONNOLLY LLP
BY: KATHRYN S. KAYALI, ESQUIRE
ANDREW V. TRASK, ESQUIRE
CHORONG SONG, ESQUIRE
680 Maine Avenue SW
Washington, DC 20024
PHONE: 202.434.5000
EMAIL: kkayali@wc.com

ALSO PRESENT:

Petra Scamborova,

Regeneron in-house counsel

Neil M. Bressler, M.D. - via Zoom

Yi Qu, Williams & Connolly

VIDEOGRAPHER:

Jonathan Juarez

- - -

TRANSCRIPT INDEX

PAGE

APPEARANCES..... 3 - 4

INDEX OF EXHIBITS..... 6 - 7

EXAMINATION OF DONALD J. D'AMICO, M.D.:

BY: MS. KAYALI..... 11

BY: MS. CHACON..... 447

BY: MS. KAYALI..... 458

AFTERNOON SESSION..... 226

EVENING SESSION..... 412

EXHIBITS WITH ORIGINAL TRANSCRIPT

- - -

- - -

E X H I B I T S

- - -

NO.	DESCRIPTION	PAGE
D'Amico Exhibit 2041	D'Amico article, American Journal of Ophthalmology August, 1985	79
D'Amico Exhibit 2042	Talamo article, American Journal of Ophthalmology, December, 1985	95
D'Amico Exhibit 2043	Oum article, Graefe's Archive For Clinical and Experimental Ophthalmology 1992	106
D'Amico Exhibit 2044	Sakarya article European Journal Ophthalmology 2010	124

- - -

E X H I B I T S

- - -

NO.	DESCRIPTION	PAGE
D'Amico Exhibit 2045	Macugen Highlights of Prescribing Information, Bates ALVOTECH 1048	247

(REPORTER'S NOTE: All quotations from exhibits are reflected in the manner in which they were read into the record and do not necessarily denote an exact quote from the document.)

DEPOSITION SUPPORT INDEX

DIRECTION TO WITNESS NOT TO ANSWER

Page Line

- -none- -

REQUEST FOR PRODUCTION OF DOCUMENTS

Page Line

- -none- -

STIPULATIONS

Page Line

- -none- -

QUESTIONS MARKED

Page Line

- -none- -

- - -

9:11 a.m. EST

New York, New York

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THE VIDEOGRAPHER: We are now on the record.

My name is Jonathan Juarez. I am a legal videographer for Digital Evidence Group. Today's date is June 2nd, 2026, and the time is 9:11 a.m.

This deposition is taking place at 7 Times Square, New York, New York, in the matter of Alvotech versus Regeneron. The deponent is Dr. Donald D'Amico.

Counsel, please identify yourselves for the record.

MS. KAYALI: Good morning. My name is Kathryn Kayali on behalf of patent owner Regeneron, and -- I'm of Williams and Connolly, and with me today are Andrew Trask and Chorong Song, both with Williams and Connolly, and also Yi Qu who is a summer associate at Williams and Connolly,

and Petra Scamborova who is in-house counsel for Regeneron. And then from time to time, we may get a guest appearance from Dr. Bressler, who is not a lawyer, but is a practicing retinal physician.

MS. CHACON: Megan Chacon from Fish and Richardson on behalf of petitioner Alvotech and the expert witness, Dr. Don D'Amico.

THE VIDEOGRAPHER: The court reporter is Marie Foley, and will now swear in the witness.

THE STENOGRAPHER: If I could ask you to raise your right hand, please.

Do you swear or affirm the testimony you give will be the truth, the whole truth, and nothing but the truth today?

THE WITNESS: I do.

THE STENOGRAPHER: Thank you.

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DONALD J. D'AMICO, M.D., the Witness herein, having been first duly sworn by a

Notary Public in and of the State of New York, was examined and testified as follows:

EXAMINATION BY

MS. KAYALI:

Q. Good morning, Dr. D'Amico.

A. Good morning.

Q. So, as we just said, my name is Kat Kayali. I'm a lawyer at Williams and Connolly, and I represent Regeneron. There's quite a cast of characters also here with me today.

Is this your first deposition?

A. No.

Q. How many times have you been deposed before?

A. Approximately a dozen.

Q. A dozen.

In -- in patent cases?

A. I've worked on patent cases, but never got to a deposition, but mainly medical malpractice, practice issues, things like that.

Q. I see.

Is this the first time you've

ever submitted an expert declaration or an expert report?

A. Yes.

Q. And is this the first time -- sorry. So it's the first time -- must be the first time in a patent case, right?

A. What do you mean by -- I have -- like I said, I've worked on other patent cases, but never reached the point of a declaration.

Q. Okay.

And declaration, that's the written paper, right?

A. Correct.

Q. Okay.

Do you recall a case called John Hopkins versus Alcon Labs?

A. Yes, that's the one I'm referring to.

Q. Okay.

And you didn't submit any report in that case?

A. No. That case was settled. I don't recall the paperwork that was ultimately submitted, but the Al -- there

was a settlement of that case, and it never went to trial.

Q. Never went to trial.

Do you remember if you had to sit in a room like this and get deposed?

A. No, I don't remember.

Q. You don't --

A. I don't believe I was deposed in that case.

Q. Okay.

And you don't believe you submitted a report or a declaration along the lines that you submitted in this case?

A. There were -- there were certainly documents, but whether it was a declaration, I don't recall.

Q. Got it.

So you were -- you were responsible for some documents, just can't remember --

A. Correct.

Q. -- what they were. Okay.

(Stenographer instruction on cross talk.)

Q. Okay. So, some ground rules.

Madam Court Reporter just took care of the first one for me, which is to please, if you can, try and let's not talk over each other. It's tough. It's a long day. If -- you know, we'll -- we'll start out great at it and then we'll get worse at it as the day goes on. That's natural. I'm sure Madam Court Reporter will remind us, but as you can see, she is taking down what we say here today, and so it's important that we get audible answers to the questions rather than a nod or a mm-hm.

And from time to time, your attorney may object to a question I asked, but you might notice here there's no judge in the room. So the objections are for the lawyers to argue about later. For today, the rules are that you're supposed to answer my question even if your attorney objects.

Do you understand?

A. Yes.

Q. Okay.

I'm going to do my level best to

ask as clear a question as I can. I think we're going to find out pretty quickly that you're a doctor and I'm not, and so from time to time, I may, kind of, bungle something. If you don't understand my question, will you please let me know?

A. Yes.

Q. Okay. If you tell me you don't understand, I'm going to do my best to get to the bottom of why, but otherwise, if you answer my question, I'll assume you understood it.

Is that fair?

A. Yes.

Q. Okay.

There's a court reporter a videographer in the room. The court reporter is taking down your testimony, and she's just sworn you in. So do you understand that you're under oath?

A. Yes.

Q. Which means you're under penalty of perjury, right?

A. Yes.

Q. And you also understand that

your name and whatever you say here today eventually will become publically available on the internet, right?

A. Yes.

Q. Okay.

Do you know Dr. Neil Bressler?

A. Yes.

Q. Who is he?

A. Dr. Neil Bressler is a professor of ophthalmology at Johns Hopkins University and one of my former trainees.

Q. Dr. Bressler is well-respected in the field?

A. Completely.

Q. Any reason you couldn't testify truthfully and to the best of your ability today?

A. No.

Q. Okay.

No medical issues, no medication, nothing like that that causes a problem sitting here for seven hours today?

A. No.

Q. Okay.

So, how did you come to be involved in this case?

A. I was -- as I recall, I was -- Alvotech inquired if I might be available as an expert -- provide expert testimony relating to an issue of macular degeneration.

Q. And was it someone at Alvotech who reached out or a lawyer at Fish and Richardson who reached out?

A. No, it wasn't Alvotech. It was Fish and Richardson. Excuse me, that was a misstatement.

Yes, it was Fish and Richardson. I had no knowledge of a company called Alvotech prior to being in -- involved in this case.

Q. Do you recall who at Fish and Richardson reached out to you?

A. I don't.

Q. All right.

A. It could have been -- it could have been Counsel Chacon next to me or it could have been another attorney.

Q. Okay.

Have you ever worked with attorneys at Fish and Richardson before?

A. Not to my knowledge.

Q. Okay.

Do you recall in the earlier case that you did, that Alcon case, whether Fish and Richardson was representing the -- the party that you were engaged by?

A. The -- they were -- no, they weren't. It was a firm in Chicago whose name I don't recall. The principals were in Chicago that I worked with.

Q. Got it, okay.

Okay. So, someone at Fish and Richardson reached out to you.

Do you recall when that was?

A. Year-and-a-half to two years ago would be my best recollection. I don't know.

Q. Okay.

So, you'll -- you signed your declaration on September 17th, 2025, so that is more than six months ago at this point.

Do you recall how long before that you were engaged?

A. A number of months. I would need to check emails and things like that to come up with a more precise, but there were substantial discussions prior to -- you're asking how long was I engaged prior to creating a written declaration? Is that your question?

Q. That's my question, exactly.

A. Okay.

It was -- it was certainly more than six months but less than two years. I -- that would be the best I would be able to give you.

Q. Okay.

What's your understanding of why you're here today, why -- why we're having this deposition?

A. My understanding is that I am here to represent a person of ordinary skill in the art who would have been able to have a reasonable chance of success at creating a new formulation of a higher dose of a VEGF Trap protein for use in

patients with age-related macular degeneration.

Q. Okay.

How did you prepare for today's testimony?

A. Extensively. I reviewed various documents. I reviewed -- I participated in numerous preparatory calls with the team, the multidisciplinary team. I engaged in numerous conversations and exchanges with counsel. I reviewed the relevant literature, and I also utilized recollections from conferences and my general fund of knowledge being a practitioner in this field.

Q. Okay. And you said you had extensive -- sorry, numerous preparatory calls with the multidisciplinary team.

What did you mean by that?

A. Please explain your question, because to me it sounds obvious.

Q. Okay.

What -- what multidisciplinary team were you referring to?

A. So, in the -- in the team, there

was not only counsel, but there was a formulation expert, Dr. Falconer. There were various other people, that I will not detail, within Fish and Richardson, because I believe that information regarding our process is proprietary. And literature reviews, et cetera.

So I think that that's my definition of multidisciplinary team.

Q. So, are you referring to the -- the -- let me -- let me ask a different question.

When you prepared for your deposition today, I'm not talking about the document that you signed, I'm talking about the time after you signed the document until today preparing for sitting here and answering questions today, about how many meetings would you say you had after you signed your declaration?

A. I don't understand your question.

My preparation -- is your question simply a per-hour post-document signing to now, or do you want me to

comment on what I consider preparation for being here? Because those are distinct. Preparation for being here would include, you know, studying for medical school and all of those things.

Q. Sure.

A. So please clarify your question, if I may.

Q. Of course.

So, all I'm thinking about is did you meet in the last couple of days with attorneys from Fish and Richardson?

A. Yes.

Q. Okay.

For how long?

A. Eight hours.

Q. When was that?

A. Over the last several days.

Q. So eight hours, kind of, chopped up into different --

A. Yes.

Q. -- time frames?

You're a practicing clinician, right?

A. Yes.

Q. So you have to squeeze in prep sessions in between your --

A. Correct.

Q. -- other work. Okay.

Who was there at those meetings?

A. Various members of the Fish and Richardson team.

THE WITNESS: May I enumerate them?

MS. CHACON: Yes, you can.

A. Megan Chacon, Michael Kane, Kristi whose last name I do not recall. And there may have been other people involved.

Q. Okay.

Were those meetings in person or by Zoom?

A. Both.

Q. And you think sum total about eight hours, you said?

A. Could be ten. Could be ten.

Q. Give or take.

A. Something like that, yeah.

Q. Rounds to ten?

A. Yeah.

Q. Okay. Fair enough.

And in those meetings, did you review documents?

A. Yes.

Q. I assume one of those documents was your declaration, right?

A. Yes.

Q. Did you review any documents that weren't cited in your declaration?

A. Not to my knowledge.

Q. Okay.

Who's Dr. Falconer?

A. Dr. Falconer is a drug formulation expert.

Q. Okay.

Have you ever spoken to him?

A. Yes.

Q. When?

A. I would have to refresh my memory on that. The date is given in my declaration, so it would take me some time to find it, but...

Q. Okay. Let's think about just relative time.

So, you signed your declaration

on September 17th, 2025.

Do you recall whether you spoke to him shortly before that, months before that, days before that?

A. It was shortly before my declaration, but certainly information about the themes and the lines of thinking were being shared within our process at Fish and Richardson much before that.

Q. I see.

Did you review a -- did you review Dr. Falconer's declaration?

A. Yes.

Q. When did you receive that?

A. I don't recall.

Q. Do you recall whether you received it after he signed it?

A. I don't recall.

Q. Okay.

Do you recall whether you received it more than a day before --

A. I don't recall.

Q. Well, can I finish my question first?

A. Sure.

Q. Sorry.

Did you receive it -- did you receive Dr. Falconer's declaration more than 24 hours before you signed your declaration?

A. I don't recall.

Q. Don't recall.

Do you recall whether it was more than a week before you signed your declaration?

A. I don't recall.

Q. Do you recall whether it was before you started writing your declaration?

A. I don't recall.

Q. So you don't recall whether you read Dr. Falconer's declaration before you put pen to paper on your declaration?

A. No.

MS. CHACON: Objection; asked and answered.

THE WITNESS: Yeah, I've answered that question already.

MS. KAYALI: Sorry, I -- I don't think you have.

BY MS. KAYALI:

Q. Before you put pen to paper on your declaration, had you read Dr. Falconer's declaration?

A. Yes.

Q. Okay.

And so you put pen to paper in -- on your declaration after having reviewed Dr. Falconer's opinions in his declaration?

MS. CHACON: Objection; asked and answered.

BY MS. KAYALI:

Q. Was that a "yes"?

A. Yes.

Q. Okay.

And you have no recollection sitting here today whether or not his declaration was signed by him when you were reading it?

A. That is correct.

Q. Do you know whether Dr. Falconer has been deposed in this case?

A. Yes.

Q. Have you reviewed -- sorry,

what -- what is the answer? Has he been deposed?

A. He has been deposed.

Q. Okay.

And did you review the transcript of his deposition?

A. No.

Q. When's the last time you looked at Dr. Falconer's report?

A. I've reviewed elements of Dr. Falconer's report as contained in my declaration, but his full declaration, I can't recall the last time I reviewed it.

Q. And you testified earlier that you didn't put pen to paper on your declaration until after you had read his declaration, right?

A. Correct.

MS. CHACON: Objection; mischaracterizes the witness's testimony.

THE WITNESS: Pardon?

MS. CHACON: I'm just objecting.

THE WITNESS: Yes.

BY MS. KAYALI:

Q. And that makes sense because some of your opinions rely on his opinions, right?

A. Correct.

Q. And you had to wait to understand what his opinions were so that you could form your own opinions, right?

A. His opinions were largely known to me prior to his declaration. So, yes, I was relying on his opinion.

His declaration was only one element of the information that I obtained from Dr. Falconer.

Q. Okay.

What other information did you obtain from him?

A. Through communications with Fish and Richardson about various --

MS. CHACON: And, Dr. D'Amico, I'm going to instruct you not to answer any attorney/client privilege information.

You can talk generally about your communications with Dr. Falconer,

but I'm going to instruct you not to answer any communications with Fish and Richardson.

BY MS. KAYALI:

Q. Okay.

So, my question is simply, let's say, when in drafting your declaration did you become aware of what Dr. Falconer's opinions were?

A. Before that point.

Q. Okay.

And you became aware of them through reading his declaration or through speaking with him?

A. It wasn't one or the other.

Q. Both?

A. Correct.

Q. Okay.

And you had to wait until you understood his opinions to form your opinions because your opinions rely on his opinions. Otherwise you'd have prejudged the issue, right?

A. Please rephrase --

MS. CHACON: Objection; vague.

A. Please rephrase your question.
Q. So --
MS. KAYALI: I'll strike that.
Q. Okay.
You understand this is a case about Regeneron's patent, right?
A. Yes.
Q. Okay. And I'm going to hand you that patent. It's number 12,168,036.
This does not need a sticker. This is already in this proceeding as 1001. And, Dr. D'Amico, I'm talking about the number at the bottom left-hand corner when I say that.
Do you recognize this document?
A. Yes.
Q. If I from time to time call this document "the '036 patent" or "Regeneron's patent," will you know what I'm talking about?
A. Yes.
Q. You'll know that I'm talking about Exhibit 1001, just for the court's records?
A. Yes.

Q. Okay.

So, taking a look at the '036 patent, do you understand that if you turn to the last page, it's pages 78 through 79, there are a number of claims of the patents?

A. Yes.

Q. Okay.

What were you asked to do in this case with respect to the '036 patent?

A. Could you -- could you narrow that question? Because there -- I don't understand beyond the scope of the question.

Q. Okay.

So, you were engaged by counsel for Alvotech, right, as an expert?

A. (Nodding.)

Yes.

Q. Sorry, you have to say "yes." Okay.

And what did they ask you to do?

A. They asked me to evaluate the claims of the patent and to determine if these claims in this patent were invalid

by reason of obviousness.

Q. Okay.

So, you looked -- you started by looking at what the claims of the '036 patent require, right?

A. The word "starting," no.

I probably started with a general discussion about macular degeneration, but with regard to the patent, yes, the claims were a central point of it.

Q. Okay.

So, what did you do after you read the claims of the patent?

A. A lot of things. I'd have to know what -- I mean, read. I engaged in discussions. I studied, had conversations.

So, I -- what -- what exactly are you referring to what did I do? You want all of those?

Q. Maybe let's take it step-by-step.

So, you were asked to determine whether the claims of the patent were invalid by reason of obviousness. So the

first step in that analysis was reading the claims of the patent?

A. Not necessarily. I also need -- required instruction about what a person of ordinary skill in the art is and to familiarize myself with your world, that is the world of patent law.

Q. Got it.

So first you had to understand what the inquiry was all about, the legal inquiry was all about?

A. Yeah, was I a suitable -- would I be a potentially suitable expert for this material.

Q. I see, okay.

And so once you -- did you conclude that you were?

A. Yes.

Q. Once you had reached that conclusion, and you set out to determine whether the '036 patent was invalid for obviousness, after you had read the claims of the '036 patent, what did you do next?

A. After I had read the claims, I evaluated pre-existing information and

began collaboration with counsel to clarify whether these claims would have been obvious to a person of ordinary skill in the art.

Q. I see.

And I assume that involves some, like, searching for prior art, right?

A. Correct.

Q. Okay.

So it was your job to go read the claims and then figure out whether all the pieces of the claim were in the prior art?

MS. CHACON: Objection; calls for legal conclusion.

A. I -- could you restate the question?

Q. Sure.

So, you said you read the claims and then you did some searching.

What were you searching for?

A. Searching for information within myself as a practitioner in the field, within published references, within prior patents, et cetera, that related to the

claims.

Q. I see.

And so you were using the claims as a guide for your search for things like, I don't know, 8 milligrams and -- of aflibercept or concentrations of the -- of fusion proteins?

MS. CHACON: Objection; mischaracterizes witness's testimony; calls for legal conclusion.

A. Correct. I -- you say "you're using the claims as a guide." I don't under -- I -- this is -- relates to general information also about the treatment of macular degeneration, diabetic macular edema, diabetic retinopathy, proliferative retinopathy, branch retinal vein occlusion, central retinal vein occlusion. And there's an enormous body of information available to a person of skill in the art such as me that can be brought to bear on reading these claims. So it isn't as though the claims are the key to my understandings regarding the issues surrounding the '036

patent.

So I -- that's how I would like to answer that question.

Q. Okay. So, I think we're saying the same thing, but maybe let me see if I can clarify.

So, I completely understand that you came to this case with an immense body of knowledge about anti-VEGF agents probably, right?

A. Yes.

Q. And about AMD and DME and retinal vein occlusion, right?

A. Yes.

Q. Okay. So, I'm talking about what happened after that.

After you were engaged by counsel, after you read the claims of the '036 patent, you said you did some searching. I'm trying to understand how you knew what to search for.

MS. CHACON: Objection; vague.

A. Yeah, items related to the '036 patent.

Q. Okay.

And when you say "related to the '036 patent," let's just -- for example, was one of the things you searched for 8 milligrams of aflibercept?

A. Yes.

Q. Okay.

And was one of the authentication you searched for documents that disclosed pharmaceutical formulations comprising at least 100 milligrams per milliliter of fusion proteins?

A. Among other things, yes.

Q. Okay.

And was one of the things you searched for references disclosing protein formulations with a viscosity of about 5 to 15 centipoise?

A. Yes.

Q. Okay.

Is one of the things you searched for a -- whether there were any references that disclose an injection volume of 70 microliters?

A. Yes.

Q. Okay.

Was one of the things you searched for whether any reference disclosed 114.3 milligrams per milliliter of aflibercept?

A. Yes.

Q. Okay.

And you knew to search for those things because they're written in the claims of the '036 patent, right?

MS. CHACON: Objection; asked and answered; calls for legal conclusion.

A. Yes.

Q. Okay.

Okay. So, I understand counsel has placed an unmarked copy of your report in front of you, right?

Excuse me. I say "your report." Technically, technically it's a declaration, but if I say "report," will you understand I'm referring to your declaration?

A. I understand that "declaration" and "report" are the same thing.

Q. Legally technically slightly

different, but for today's purposes, I think we can handle that.

I'm going to just, so that we're all looking at exactly the same document, hand you another copy of your report. It's not any more exciting.

Well, I don't mean to say your report is not exciting. It's not any different than that one.

Okay. And this is Exhibit 1003.

MS. KAYALI: I'm sure you've never seen that one before, right?

BY MS. KAYALI:

Q. Okay.

Can you turn to page 184 of your declaration?

Are you there?

A. Yes.

Q. Okay. Do you see that you -- well, let me ask a better question.

It's a little confusing at -- in this declaration. Do you see at the bottom of the page there's the number 183 and the number 184?

A. Yes.

Q. I'm going to do my very best to use the -- the numbers that are further down the page, the 184 number. When we are in your declaration, I'll be able to talk about paragraphs, but if we're talking about page numbers, I'm going to try and use that one.

Does that make sense?

A. Yes.

Q. Okay.

So, on page 184, is that your signature?

A. Yes.

Q. Okay.

And did you sign in wet ink, or did you use a digital signature?

A. Digital signature.

Q. Okay.

And did you send that to counsel and they applied it, or did you apply it?

A. I don't recall.

Q. Okay.

And am I correct in understanding that you provided your signature authority on September 17th,

2025?

A. Yes.

Q. Okay.

And that was the day that you signed off on what was in your report?

A. Yes.

Q. Okay.

And if you turn to the preceding page, do you see paragraph 391?

A. Yes.

Q. You say: I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code.

Do you see that?

A. Yes.
Q. I read that correctly?
A. Yes.
Q. Okay.
And do you understand what that means?
A. Yes.
Q. What does it mean?
A. It means that I'm attesting that not only is it a truthful declaration, but there are substantial penalties if it is not a truthful declaration.
Q. Okay.
Do you recall what time of day you signed your report?
A. No.
Q. Do you recall whether it was, like, in the morning or nearly midnight?
A. I've already answered that I don't recall.
Q. Okay.
Do you -- do you typically stay up until midnight?
A. I don't have a typical. I'm a surgeon and there's no typical.

Q. Fair enough.

Were you awake at midnight any time in the last week?

A. I don't recall.

Q. You don't recall sitting here today whether any time in the last week you were awake at midnight?

A. No. I may have --

MS. CHACON: Objection; asked and answered.

A. I've answered the question.

Q. Okay. And what is the answer?

A. I don't recall.

Q. This week whether you were awake past midnight?

A. Yeah. I mean, it is entirely possible that I woke up in the middle of the night for 30 seconds, turned over and was awake at midnight. It's entirely possible that I wasn't. But I do not recall specifically in this week whether I was awake at midnight.

Q. Okay. Let me -- sorry. That's fair. Let me ask a better question.

At any point this week, did you

go to bed after midnight?

A. I don't recall.

Q. Do you -- you don't recall whether you went to bed after midnight or not --

A. I don't recall.

Q. -- this week?

Okay.

Do you recall whether you went to bed after midnight yesterday?

MS. CHACON: Objection; asked and answered.

Counsel, what's the relevance of this?

MS. KAYALI: Because it's --

MS. CHACON: Because it's getting to the point of harassing the witness asking him over and over what time he went to bed. He's already answered the question.

MS. KAYALI: Counsel, you're aware of what the Trial Practice Guide stipulates regarding objections in these proceedings. They're to be one word.

If this continues, we'll just call the board.

MS. CHACON: Be my guest, but I'm not going to allow you to harass the witness.

So you can proceed with your question, but I would ask you to take that in consideration.

Go ahead.

BY MS. KAYALI:

Q. Do you recall yesterday whether you went to bed before midnight?

A. I don't recall.

Q. Okay.

So, you don't recall whether you signed this declaration early in the morning or late at night, right? That's what you said?

A. If you're asking me do I recall what time of day I signed this declaration, I've already answered that I do not recall.

Q. Okay.

This language suggests to me that you signed the declaration outside

the United States.

Were you located inside the United States or outside the United States when you signed this?

A. I don't recall. I would need access to my calendar.

Q. Okay.

Do you recall whether you made -- were traveling abroad at any time in September of last year?

A. I don't recall.

Again, I would need -- I have an active calendar and would need access to it in order to answer your question specifically.

Q. Do you frequently travel abroad?

A. Yes.

Q. Okay.

Could you -- sorry. You've reviewed your declaration in preparation for today's testimony. I think you've already testified to that, right?

A. Yes.

Q. In doing so, did you identify any mistakes you'd like to correct?

A. No.
Q. Okay.
Could you turn to paragraph 15, please?
Okay. Paragraph 15 -- excuse me, I misspoke. Paragraph 13.
Do you see the paragraph 13 is the first paragraph under "Summary of Opinions"?
A. Yes.
Q. Okay. And you provide an opinion -- or, let me ask a better question.
This section is you're aware you provide a summary of opinions you've offered in your declaration, right?
A. It's titled "Summary of Opinions." Yes.
Q. Okay.
And -- and it -- that title is accurate, right?
A. Yes.
Q. Okay.
You have an opinion with respect to Ground 1 in paragraph 14, right?

A. Yes.
Q. And you have an opinion with respect to Ground 2 in paragraph 15, right?
A. Yes.
Q. And you have an opinion with respect to Ground 4 in paragraph 16, right?
A. Yes.
Q. And you have an opinion with respect to Ground4 5 in paragraph 17, right?
A. Yes.
Q. Okay.
You do not have an opinion with respect to Ground 3, right?
A. Correct.
Q. Okay. Could you turn to paragraph 12, please?
You say: In writing this declaration, I have relied on my background, education and experience as a physician both in treating patients with angiogenic eye disorders and studying the treatment of such disorders in clinical

trials. I also rely upon a discussion with Dr. Robert Falconer that took place on June 16th, 2025. I have also considered, in whole or in part, the following documents forming my opinion in this matter.

Did I read that correctly?

A. Yes.

Q. Okay.

And then you have a table of documents, right?

A. Yes.

Q. And this table accurately lists all the documents that you considered in forming your opinions, setting aside your -- the knowledge you already came to the table with?

A. Setting aside the knowledge I already came to the table with, yes.

Q. Okay.

So you didn't specifically review any documents outside the ones listed here in order to form your opinions, otherwise you would have listed them?

A. Correct.
Q. Okay.
Can we turn to the discussion with Dr. Falconer?
When did that discussion take place?
A. It states June 16, 2025.
Q. Okay.
Did you speak to Dr. Falconer once, twice?
It says only once, right?
A. Correct.
Q. Okay.
And that's consistent with your recollection?
A. Yes.
Q. Okay.
You said earlier, I believe, that you conversed with Dr. Falconer very, I think -- I have to go back and check, but in close proximity to the time you signed your declaration, right?
MS. CHACON: Objection; mischaracterizes testimony.
A. Yes.

Q. Okay.

Does that June 16, 2025 date sound right to you?

A. I would have to have access to my calendar, but it seems about right.

Q. Okay.

And you received Dr. Falconer's declaration after you spoke with him, right?

A. I don't recall that.

Q. You don't remember one way or the other?

A. Correct.

Q. So, you testified earlier that you had not reviewed Dr. Falconer's deposition transcript, right?

A. Correct.

Q. Are you -- so you're not aware then Dr. Falconer testified that actually your conversation took place on September 16th, 2025?

A. I'm not aware of that.

Again, I would need access of my calendar to verify specific dates, as I have mentioned.

Q. Okay. But you only spoke once, and he says it happened in -- on September 16th, 2025, and you say it happened on June 16th, 2025, and I need to know when it happened.

So, what's your answer to that?

A. I would need access to my calendar to verify the date the conversation took place.

Q. Okay.

And would you also need access to your email to figure out what time -- or, sorry, when in relation to that conversation you received his declaration?

A. Yes.

Q. And you would need access to your email to determine whether when you received the declaration it was signed?

A. Yes.

Q. Okay.

And that's how this communication was done; it was done by email, right?

A. Yes.

Q. Okay.

You would not -- well, you testified earlier that you needed --

MS. KAYALI: Let me strike that.

Q. Document Number 1004 is the declaration of Dr. Robert J. Falconer, right?

A. Yes, so listed.

Q. Okay.

And if you listed that there, you must have read the whole thing, right?

A. Yes.

Q. Okay.

And there are numerous citations to Exhibit 1004 throughout your declaration.

Did you add those after you read the declaration?

A. I'm not aware of the timing of those additions. They could have been before the declaration was read as part of preparatory work as a multidisciplinary team, or it could have been after.

I don't know the timing. I can't recall.

Q. So, when you say "the

multidisciplinary team," are you suggesting that Dr. Falconer wrote portions of your report?

A. No.

Q. Okay.

When you say "multidisciplinary team," are you just saying the lawyers wrote portions of your report?

A. No.

MS. CHACON: Objection; mischaracterizes testimony.

A. No. I'm saying it was a collaborative effort.

Q. It was a collaborative effort, and irrespective of the numerosity of citations to Exhibit 1004 in your declaration, you don't recall whether those were added after you knew what the declaration said?

A. I -- I don't understand your question.

Please rephrase.

Q. Were the -- did you add your citations to the declaration of Dr. Falconer before or after you had read

it?

A. Did I add the citations to Dr. Falconer?

The actual numerical citations, the referencing were only possible after the document, of course, existed in final written form, but the -- the information avail -- was available substantially prior to the creation of his written document.

Q. So, you put opinions in your report that relied on Dr. Falconer's declaration without knowing what the final thing said?

MS. CHACON: Objection; mischaracterizes testimony.

A. I -- I -- yeah, I might well know what the final thing said. It just might not exist in written form in his declaration. He could have made a conclusion about a certain element months before his written declaration was written and we would be -- utilize that as working knowledge, and simply the referencing would be the only part that would be -- require reading of his document.

Q. And you knew what his opinions were before reading his declaration because he conveyed them to you in a conversation?

A. Because of a collaborative process that -- of the multidisciplinary team, yes.

Q. And so, when you say "multidisciplinary team," you are including lawyers in that team, right?

A. I have already indicated what a person of ordinary skill of the art is, and if you'd like, I'm happy to reference that section in my declaration.

Q. So, that's why I'm a little confused.

You -- is it your opinion that lawyers are part of the person of ordinary skill in the art?

A. No.

Q. Okay.

When you say "the multidisciplinary team," are you talking about a person of ordinary skill in the art, or are you talking about all the

people that worked on your declaration?

A. Neither.

I'm talking about the combination of a person of ordinary skill in the art such as pertains to a medical physician, surgical physician related to macular degeneration, or another professional who might be an expert, say, in formulation chemistry.

Q. Okay. But here's what I'm trying to understand.

How were Dr. Falconer's opinions conveyed to you before signing -- before you read his declaration?

MS. CHACON: And before you answer, Dr. D'Amico, I'm going to caution you not to reveal the substance of any communications with counsel that are covered by privilege.

If you can answer the question without doing that, please proceed.

A. Yeah, there were -- there were communications available to me prior to the signing of -- prior to his -- my receiving his signed declaration.

Q. What kind of communications?
A. Emails, conversations, et cetera.
Q. With Dr. Falconer?
A. Again, I'm not at liberty to say the --
Q. Well, that one you are at liberty to say. I'm asking whether you got the information about Dr. Falconer's opinions from Dr. Falconer or from lawyers.
A. I received Dr. Falconer's final report and had a single conversation with him on a date that we have already discussed, which is apparently indeterminate.
The information relating to his conversations was subsumed into part of the preparation for this -- for this declaration.
Q. And that means that before Dr. Falconer told you what you thought -- what he thought, the lawyers told you what he thought?
MS. CHACON: Objection;

mischaracterizes testimony.

A. Yes.

Q. Okay.

You mentioned the date is indeterminate.

Your declaration says it took place on June 16th, right?

A. Yes.

Q. Let me ask a better question, sorry.

You said the date of your conversation with Dr. Falconer is indeterminate, right?

A. Yes.

Q. And your declaration says it took place on June 16th, 2025, right?

A. Right.

Q. And he says it took place on September 16th, 2025, right?

A. I would have to see the reference for that, but I believe it was shown previously to me.

Q. Sorry, what was shown previously to you?

A. The -- that where he states it

took place. Was it shown -- where -- where is that information that he's asserting that it takes place on September --

Q. Maybe we're just confusing each other.

I haven't shown you a document that says that. I'm just telling you that he testified to that effect.

A. I have no means to verify or dispute the information you're providing me now.

Q. Okay. And I'll also represent to you that means -- I'm not going to take the time to show you the document, but I'm telling you what it says. I'll represent to you that his declaration says this conversation, this one conversation, took place on September 16th, 2025.

So that's different from what your declaration says, right?

A. Yes, clearly.

Q. Okay. You have -- I think you've said this, but I just want to make very sure.

You have no recollection of whether you had this conversation the day before you signed your report or three months before you signed your report, right?

A. I -- I have no recollection.

I recall it was in proximity to the time of my signing the report, but I have no recollection with precision.

Q. Okay.

Do you consider three months to be within proximity of signing your report?

A. In my world, yes.

Q. You verified that all the citations and statements in your report are accurate, right?

A. Yes.

Q. Okay.

So, after you received the final copy of Dr. Falconer's report, you personally verified that everything you thought he was going to say he actually said the way you thought, right?

A. Yes.

Q. Okay.
When did you do that?
A. I don't recall.
Q. But after he signed his declaration, right?
A. I -- I don't recall.
Q. How could you have done it before he signed his declaration?
A. I may have seen a draft copy.
Q. Okay.
And you would have relied on a -- that draft copy in that case?
A. Yes.
Q. Okay.
I would like to take some time now to talk about your background. I know you address this in your report. I suspect you also know it by heart, but that's up to you.
Where did you get your undergraduate degree?
A. MIT.
Q. Okay.
And in what was it?
A. 1972. I have a degree in

chemistry.

Q. Chemistry, okay.

And then what did you do next?

A. I went to medical school.

Q. Where?

A. University of Illinois.

Q. Can you have a special in medical school? Was there -- did you specialize in anything in particular?

A. Not during medical school, no.

Q. Okay.

That's not normal. You specialize later?

A. Correct.

Q. Okay.

So what did you do after medical school?

A. After medical school, I spent some time during medical school in -- studying neurochemistry. I had a -- sort of, a year of research within medical school, and then I do an internship immediately after medical school.

Q. Okay. And I should have asked this before.

When did you graduate medical school?

A. 1977.

Q. Okay.

And then when you -- where did you do your internship?

A. At Michael Reese Medical Center in Chicago.

Q. I'm sorry, I'm just to going to reveal my ignorance.

Is a internship the same thing as a fellowship?

A. No. Internship is a -- is a period of practical training immediately -- usually immediately following medical school.

Q. Okay.

And then fellowship comes later?

A. Fellowship is usually done after a residency. So it may be --

Q. I'm missing all the --

A. -- four to seven years after a fellowship.

Q. Got it, okay. Well, then let me back up and take it piecemeal.

What was your internship in? Did you specialize in anything?

A. It was a -- a rotating general medical internship.

Q. Okay.

And then did you proceed to residency? Is that next?

A. Yes.

Q. Where did you go become a resident?

A. Harvard Medical School.

Q. And did you specialize in anything as a resident?

A. A residency is a specialization in a -- in a discipline of medicine. In my case, ophthalmology.

Q. Okay.

Are there different branches of ophthalmology you can specialize in?

A. Not during residency, but subsequently with a fellowship, one obtains specialization.

Q. Okay.

So, after your residency in general ophthalmology, what did you do

next?

A. I took a year as a vitreoretinal fellow at -- at Bascom Palmer Eye Institute, The University of Miami.

Q. Okay.

And what -- what did you do then? What -- did you specialize in anything then?

A. During the fellowship?

Q. Yes.

A. It's vitreoretinal specialty, so I was -- I specialized in medical and surgical diseases of the retina.

Q. I see.

Do you consider yourself an expert in ophthalmology?

A. Yes.

Q. Okay.

And I think we've already talked about this, but you understand from time to time if I refer to the POSA or the person of ordinary skill in the art, you -- you'll know what I mean?

A. Yes.

Q. Okay. And in this case, we're

talking about a hypothetical person of ordinary skill in the art as of May 10th, 2018.

Does that sound right?

A. Yes.

Q. Okay.

All right. Help me understand your -- let me ask a better question.

So, after your fellowship where you specialized in vitreoretinal surgery?

A. And diseases, yes.

Q. And diseases.

What did -- what did you do next?

A. I returned to Harvard and was on the faculty there for almost 25 years.

Q. Okay.

And when did you depart Harvard?

A. In November -- end of October 2006.

Q. What made you leave?

A. I was offered the chairmanship at Weill Cornell New York-Presbyterian Department of Ophthalmology, a position I currently hold.

Q. Okay.

So help me understand your day-to-day in that position. Do you treat patients?

A. Yes.

Q. How many a day?

A. It varies, but I can treat, depending on a day, 20, 40, something like that. It has changed as my -- as I have grown other responsibilities, but at some points, I was treating 60 patients a day.

Q. Okay.

And you might not treat 60 patients a day anymore, but at one time you did?

A. Yes.

Q. Do you treat fewer than that a day now?

A. Yes.

Q. When did you start treating fewer a day?

A. I -- I had a personal issue as I've aged and I have also become involved in substantial research and mentoring of young physicians and have trained a number

of colleagues who can take over my practice. So as I have done these other activities, there's less need for me to be in the clinic.

Q. I see.

About when did that change occur?

A. About two years ago.

Q. Okay.

You mentioned surgery. What kinds of surgeries do you do?

A. Complicated vitreoretinal surgery of all forms.

Q. Okay.

And your bio at Weill Cornell also mentions you do cataract surgery?

A. I do not.

Q. You do not, okay. You might want to get that fixed.

Do you ever inject drugs into patients' eyes?

A. Yes.

Q. How often?

A. Every time I'm in clinic almost without exception.

Q. Okay.

About how many injections would you say you do per day?

A. One to four.

Q. Okay.

Per week?

A. I see clinic patients two days per week, so it would be anywhere from two to six, eight injections per week.

Q. How -- what -- what -- sorry, you said clinic two days a week.

The other days of the week you're doing surgery?

A. Surgery, research, administration, mentoring, preparing for conferences, writing articles, editing articles, communicating with colleagues. The entire spectrum of a professional academic physician.

Q. Okay. You said you inject drugs when you're in clinic.

Do you ever inject drugs into the eye when you're in surgery?

A. Yes.

Q. In what context?

A. It could be for -- well, the answer will be lengthy. We utilize many drugs to control abnormal vascularization within the eye, and those can be sometimes administered at surgery as an adjuvant to control bleeding.

We also use antibiotics in the eye if the patient is being brought to surgery for an intraocular infection.

We also use anti-inflammatories injected into the eye if we're acting to control inflammation.

So intravitreal therapy is a -- is a common -- is a common procedure.

Q. Okay.

Have you ever performed cataract surgery?

A. Yes, as a resident.

Q. Okay.

Do -- are antibiotics used prophylactically in cataract surgery?

A. They are.

Q. And you also have experience administering those, right?

A. I have experience.

I also have extensive experience doing research on the subject that we're discussing, that is prophylactic antibiotics at cataract surgery for the treatment or prevention of endophthalmitis, yes.

I performed cataract surgery as a resident, as all residents do, but subsequent to my specialization, I do not perform conventional cataract surgery. I will occasionally remove the lens as part of vitreoretinal surgery, but depending on the definition of what you call cataract surgery, that might not be considered in the standard, you know, grandfather's cataract operation.

So the conversation -- the question would need for clarification for me to answer in greater detail.

Q. Got it.

Let me -- let me just make sure I understand what you're saying, because sometimes the nitty-gritty details get a little beyond me.

You -- setting aside whether you

perform cataract surgery, you do research on the prophylactic prevention of, what was the word, endophthalmitis?

A. Right.

Q. During cataract surgery?

A. I have done research on that.

Q. You have done research.

A. Right.

Q. Okay.

So you are familiar with antibiotics that are administered during cataract surgery and their doses?

A. Yes. My CV indicates articles in which I studied rabbits extensively with intravitreal drug therapy.

Q. And they're also intracameral antibiotics in cataract surgery, right? And you studied those?

A. Correct.

Q. Okay.

Are there subspecialties in retinal practice?

A. There -- it depends how you define "subspecialty."

Actually, within the discipline

of ophthalmology, none of the subspecialties have official designation. So, the -- whereas in, for example, neurology, I believe pediatric neurology is a distinct subspecialty compared to adult neurology.

In ophthalmology, our -- because we are the oldest specialty board, all of our specializations are considered as one. So the -- the fact that a person is a vitreoretinal specialist is a -- a strong conventional and practical designation with societies and all of that, but in a legal definition sense, all ophthalmologists are technically specialists of everything.

I'm not sure I'm making myself clear because it's a bizarre -- even a bizarro, you know, arabesque of the -- of how the regulatory world grew up. But I am a vitreoretinal specialist, yes. There -- we have societies. We have work-arounds to create designations that allow us to be, you know, credentialed, et cetera. But, yes, in terms of the

common state of the art, I am considered a vitreoretinal specialist.

Q. Okay.

And does your specialty differ at all from Dr. Bressler's?

A. It -- my -- we are both -- he, having been my fellow, he was a vitreoretinal trainee, so is fully able to perform complicated vitreoretinal surgery, as well as manage medical retinal conditions as a practical matter. He has gone in an exclusively medical retina definition -- direction and does not perform, to my knowledge, vitreoretinal surgery.

Q. I see.

And when you say "medical retina," what -- what do you mean?

A. Disease -- conditions of the retina that do not require surgery for their diagnosis and management.

Q. So that would be -- sorry, I'm probably oversimplifying this, but if I put surgery on the one hand, where do injections of anti-VEGF agents fall?

Those go to the medical retina side?

A. They go to everywhere. They go to everywhere.

A -- the limitation would not be related to injections at all. It would be related to other procedures.

So for example, a patient with macular degeneration presenting to me or to Dr. Bressler could be equally treated by both. Whereas a patient presenting with a retinal detachment, I would take them to surgery, whereas Dr. Bressler would refer them to a colleague.

Q. I see.

So, if someone comes to either you or Dr. Bressler with AMD and you know they have AMD, you don't need to do any further diagnosis, one potential treatment option is surgery?

A. No, no, no. You -- I -- no.

Well, there are surgical approaches that have been tried for macular degeneration, which are also documented in my CV because I've been involved in research on that. But if a

patient presents with mac -- macular degeneration, the standard of care now is an administration of an agent intravitreally, and either a medical retina specialist or a vitreoretinal surgeon could administer that therapy.

The majority of vitreoretinal specialists in the United States do both. It's a rarity for somebody to confine themselves only to medical retina specialty, to it -- to be a non-operating retinal specialist.

Q. Okay. I think -- I think maybe I've now understood the definition.

I'm just trying to understand what the difference between surgical retina and medical retina, and I -- I think the answer is that medical retina will do injections of anti-VEGF agents. Surgical retina will sometimes do that and will do other things?

A. Not sometimes. The -- medical retina is a particular subspecialty within the broader category of vitreoretinal specialization.

Q. I see.
A. So everything that a medical retina specialist can do a vitreoretinal specialist can do.
Q. Okay.
All right. Let's take a look at the next document I'm going to hand you.
MS. KAYALI: And this will be marked as a new exhibit. So I'll ask Madam Court Reporter to help me out.
(D'Amico Exhibit 2041, D'Amico article, American Journal of Ophthalmology August, 1985, was marked for identification, as of this date.)
MS. KAYALI: So, this will be marked as Exhibit 2041. And I'll hand you a copy.
Here's one for counsel.
MS. CHACON: Thank you.
BY MS. KAYALI:
Q. Okay.
Do you recognize this document?
A. I do.
Q. Trip down memory lane?
A. Yes.

Q. Okay.

When's the last time you looked at this document?

A. Fifteen years ago.

Q. Oh, wow.

All right. What is this document? What is Exhibit 2041?

A. This is a study that I performed with Loure Caspers-Velu under the guidance of several other -- collaboration of several other authors where we looked at how intravitreal amino glycoside antibiotics could affect the retina, a dose toxicity study.

Q. Okay.

What are aminoglycoside antibiotics?

A. These are commonly used antibiotics that have potency against what are called gram-negative organisms, and they're of utility in treating certain intraocular infections.

Q. Okay.

So aminoglycoside antibiotics, they're sort of a -- a class of drugs?

A. Correct.
Q. Okay.
And do they work in generally the same way?
A. Yes.
Q. Okay.
So you'd expect them all to have about the same therapeutic window and toxicity concerns, right?
A. No.
MS. CHACON: Objection; vague.
BY MS. KAYALI:
Q. Why is that?
A. Well, they're different drugs. They're -- there are differences.
The fact that they are different indicates that they may have different efficacies, different safeties, different toxicities, et cetera.
So I don't -- I don't understand the -- the assumption that they would all be the same.
Q. Okay.
You couldn't infer safety for one drug in a class based on another drug

in the class?

A. Indeed. That's the reason for the study.

Q. Okay.

And that -- that's true for all drugs, right?

MS. CHACON: Objection; vague.

A. I -- I don't know if it applies to all drugs.

Q. Could you turn to -- could you turn to page 273? Do you see the fourth line down beginning "Because an individual"?

A. Yes.

Q. It reads: Because the individual aminoglycoside antibiotics are used in different doses clinically, studies that compare the toxicities encountered with clinical therapy will not be similar to studies comparing drugs on a weight basis.

Right?

A. Yes.

Q. Okay.

What does this mean?

A. Well, if -- the drugs have different molecular weights, and they're also dosed differently, and those may not -- those dosage schedules may not be predicated on the molecular weight. They may be predicated on toxicity or bioavailability or absorption or other things. So you can't say that if I have 5 milligrams of an aminoglycoside A it's going to behave exactly like 5 milligrams of aminoglycoside B.

Q. I see.

Well, aren't they all, sort of, just dosed at the same level below the toxic point?

A. No. I -- again, dosage schedules are -- relate to many things, one of which is absorption, bioavailability.

So the clinical dosing is -- is variable, is highly variable and a complicated science in itself.

Q. Okay. And so the degree below, for instance -- well, let me ask a better question.

In this study, you were trying to figure out what the toxic levels of these various aminoglycoside antibiotics were, right?

A. Yes, and compare them. Compare them, yes.

Q. Okay.

And your point, I think, in this paragraph was that a clinical dose isn't necessarily collected to be, you know, X-fold below the toxic level. There are a lot of things that go into that.

A. I don't --

MS. CHACON: Objection; mischaracterizes the document.

A. I don't discuss the clinical dosing strategy here. I'm describing the tricks about the -- the delicacy of trying to compare them.

Q. To compare doses of one drug to a dose of a different drug in the same class?

A. To -- please rephrase your question.

It says -- may I read the

sentence again?

Q. Please.

A. "Because the individual aminoglycoside antibiotics are used in different doses clinically..."

So they're used -- they're used in different doses clinically.

"...studies that compare the toxicity encountered with clinical therapy..." okay.

Okay. So that's different than -- that's a clinical study which is not performed herein. This is an animal study.

"...will not be similar to those that look on a milligram-per-milligram basis."

Q. I see your point, okay.

You said "this is not a clinical study."

What do you mean?

A. It wasn't done in people.

Q. Wasn't done in people.

It has to be done in people to be a clinical study?

A. I think so.
Q. Okay.
Are there limitations of animal studies?
MS. CHACON: Objection; vague.
A. Of course, exclamation point.
Q. Help me understand the exclamation point.
A. Yeah, there -- the entire -- the entire pharmacotherapy is riddled with problems crossing over species differences, different organ systems, different anatomy, different metabolisms, et cetera.
I think the conversation would be quite lengthy, but there are many, many, many potential difficulties in animal studies.
Q. Okay.
So human data is more reliable than animal data for the purposes of understanding clinical dosing schedules, right?
MS. CHACON: Objection; vague.
A. Again, we utilize -- we utilize

animal studies extensively in order to get levels to begin our clinical studies, but the -- the proof in the pudding is generally considered to be a clinical trial, clinical study in patients.

Q. Okay.

Could you look at -- I'm sorry to have you skip around so much, but I just lost my place. Maybe the simplest place is to look at the -- the bolded "Summary" paragraph at the top.

A. Mm-hm.

Q. Do you see where you say: The earliest manifestations of toxicity were confined to the outer retina with each drug with lamellar lysosomal inclusions in the retinal pigment epithelium as the earliest finding.

Do you see that?

A. I do.

Q. Okay.

What's retinal pigment epithelium?

A. The retina resides on top of a supporting tissue called the retinal

pigment epithelium, and that tissue has a complex interaction with the photoreceptors, recycling vito -- vitamin A, and also photoreceptor pigments such as rhodopsin.

Q. Sorry, what was that last word?

A. Rhodopsin.

Q. What's rhodopsin?

A. It's the pigment that allows you to detect light.

Q. So our -- in order to figure out whether and at what dosage these drugs were toxic, you examined their effect on retinal pigment -- or, excuse me, retinal pigment epithelium cells?

A. No. In order to -- I examined the entire retina. The retina is a multilayered complicated structure, and the effects of these drugs did not affect the, quote, inner retina nerves and things like that. They affected the photoreceptors and outer retinal pigment epithelium primarily, and that's the statement in -- the intention and the literal understanding of the sentence that

we've just discussed.

Q. I see.

And is it bad if drugs negatively affect the retinal pigment epithelium?

A. Well, if they're used in a level where these changes occur, and that's the purpose of the study to look at a dose escalation on a milligram basis to study how they affect this area, yes, that is the point.

The title of the article is "Comparative Toxicity."

Q. Okay.

So, one way of determining -- well, let me ask a better question.

If a drug negatively affects retinal pigment epithelial cells, that can be an indication of retinal toxicity?

A. Please restate your question.

Q. Yeah. It's -- and we're getting at the limit of my scientific knowledge here.

If a drug negatively affects retinal pigment epithelial cells, that

could be an indication --

MS. KAYALI: Excuse me. Strike that.

Sometimes the science is getting me here.

Q. If a drug negatively affects retinal pigment epithelial cells, that's an indication that the drug has retinal toxicity?

MS. CHACON: Objection; vague.

Q. A particular dose.

MS. CHACON: Sorry, counsel.

A. Not in --

MS. CHACON: Objection; vague.

Just one moment, Doctor. Let me get my objections on the record.

Objection; vague.

You can go ahead and answer.

A. Not necessarily. There can be transient changes that are reversible. So the question -- your question would need to be much more specific to make a definitive statement about toxicity.

Q. Okay.

In this instance, were the

effects reversible?

MS. CHACON: Objection; vague.

A. Again, some of the doses we -- we did not study the same animal at multiple times because the animals were sacrificed. So we can infer no information about reversibility from these.

We can determine comparison based on the degree of retinal damage on a -- on a milligram basis which agent was more likely to produce these changes per milligram than other drugs, but the study is limited to that conclusion.

Q. Okay.

And when you say "these changes," you're talking about adverse effects on the -- for example, adverse effects in retinal pigment epithelial cells indicating retinal -- potential retinal toxicity?

A. Yeah, maybe I can give an example that will clarify.

Q. Sure, please.

A. Is that permitted?

Q. Please.

A. An example. So, if I'm evaluating whether a compound causes a rash and I have four different agents and I put different doses of those four different agents on your skin, on someone's skin, and determine the point at which the skin becomes red and how red it is, I can make an inference of how irritating those things are.

Whether that rash goes away is a completely different question. And so I'm only in this study looking at how these agents with an acute dose at a certain milligram level do something to the retina. Whether that goes away or whether it -- I would expect it would cause some harm, some of the changes, but I can't know until you do -- you know, the question you asked me, which is are these changes reversible, cannot be inferred from this -- from this material.

Q. I see. I think -- okay. That -- that is helpful to understand.

I think I'm probably trying to

ask a much simpler question, which is --

MS. KAYALI: Well, strike that.

Q. So, if -- were you looking at effects of these agents on viability of retinal epithelial cells? Excuse me, retinal pigment epithelial cells?

A. Define "viability."

Q. Isn't cell viability a standard measure of adverse effect?

A. I'm unaware of the standard. Maybe provide one.

I'm unaware of what you mean by "viability."

Q. Does -- viability means continued -- continuing to be alive, right?

A. They can continue to be alive and damaged and still have loss of function. They can continue to be alive and recover. They can continue to be alive for a while but prematurely die.

You would have to be more precise in the definition of what you mean by "viability."

Again, this is a -- this is an

acute study and does not provide any long-term information about -- that -- so, if you can define "viability" in the context of an acute study, I can provide a better answer.

Q. Okay. Sorry, this is where we all learn that I'm not a doctor.

Do you -- okay. I think I understand what you're saying.

If you think of cell viability of -- as measuring whether a cell is alive or dead, if a drug caused retinal pigment epithelial cells to have reduced viability, that would be an indication of retinal toxicity, right?

MS. CHACON: Objection; calls for speculation.

A. Yeah, I would -- I would say in general I would agree, but I would need to have more information to provide such a specific assent.

Q. Okay.

And do you know what mitochondrial membrane potential is?

A. No.

Q. Okay.

MS. CHACON: Counsel, we've been going for an hour and 15. I don't know if you're planning to take -- if there's a natural stopping point at some point, but --

MS. KAYALI: I defer to you, Doctor. Would you like to keep going or stop now?

THE WITNESS: No, let's continue.

MS. KAYALI: Okay.

So, I will mark -- let me make sure I got -- I'm going to try really hard not to make you go back to the documents. So I need to figure out whether I looked at all the documents.

Okay. So let's take a look at another document. Okay. I am going to hand you what I think will be marked as Exhibit 2042.

(D'Amico Exhibit 2042, Talamo article, American Journal of Ophthalmology, December, 1985, was marked for identification, as of this

date.)

BY MS. KAYALI:

Q. Okay.

Do you recognize this document, Dr. D'Amico?

A. I do.

Q. Okay.

What is it?

A. It is an -- an experimental study in -- studying the effect of surgical state of the eye on the retinal toxicity of intravitreal antibiotics that I performed with Dr. Talamo and other collaborators.

Q. Okay.

What does "surgical state of the eye" mean?

A. If you have removed portions of the eye or altered the eye in some way, then obviously many things are changed from a perspective of therapy with intravitreal drugs such as the distribution space of the drug. If the lens is removed, for example, and replaced with -- now with aqueous humor, that is a

bigger space for the -- for the eye. It's also will change the clearance of the agents from the eye.

You know, so those are all -- that's what I mean by the surgical state of the eye.

Q. Okay.

A. Aphakia is lens removal post cataract surgery and vitrectomy is removal of the vitreous gel.

Q. You mentioned that removal of the lens or removal of the vitreous can change clearance of the agents from the eye.

What does that mean?

A. Well, when you inject something in the eye, you have the initial dose. So all of those molecules are present in the eye at the beginning, and then the body's mechanisms, either out through the trabecular meshwork or other ways, the same way we process aqueous humor across the eye, will clear the drug, much like your kidneys or your liver will clear a systemic agent.

And altering the eye will theoretically change that clearance rate. So that's only one of the factors involved. That's the point of this study. Drugs are sometimes used in patients who have had cataract occurring or vitrectomy, and the goal of the study was to see if we can understand would altering the surgical state of the eye change the profile in animals on an acute study for the determination of retinal toxicity.

Q. What's the trabecular meshwork? Did I get that right?

A. Yes.

The trabecular meshwork is a structure at the front edge of the iris near the edge of the cornea inside the front chamber, or anterior chamber, of the eye, and it's the drain by which the flow of glaucoma fluid or aqueous humor leaves the eye. It's also the drain by which many substances injected into the eye, whether in the vitreous or in the anterior chamber, will exit the eye.

Q. So why does it matter how

quickly a drug is cleared from the eye?

A. Because some drugs will have their toxicity evidenced by the residence time of the drug. If it -- the drug is injected and it's gone from the eye in two minutes will have a completely different -- potentially completely different toxicity profile than a drug that's injected and resides in the vitreous for two weeks.

In this particular study, acute, for these particular agents, we determined that the clearance was actually not a factor in this particular class of -- in this particular drug because the toxicity appeared to be consistent with whatever the peak dose was reached regardless of how long the residence time of that drug was in the vitreous cavity. It will be different for different drugs.

Q. And you didn't -- is that what you expected?

A. I didn't have a -- I -- I wanted to know the -- I wanted to know the conclusion of this study one way or the

other. If it -- if it said that the toxicity was much, much lower because the drugs were eluding from the eye, washing out from the eye faster, then maybe we would have formulated a clinical recommendation to use a higher dose in patients who's had surgery on their eye already.

But this study said don't do it. Even eyes that have had vitreous and -- and lens removed still will evidence toxicity related to the peak concentration of the drug.

Q. What determines a peak concentration of the drug?

A. How much you have in the syringe and the size of the volume into which it's being injected.

Q. So the starting dose?

A. The starting -- yeah, peak concentration would be the starting dose entered into whatever the medium is in which you're injecting.

In a rabbit eye that's approximately 1, 1 1/2 milliliters. In a

human eye it's approximately 4 milliliters. So the concentration, which is the word in your question, would differ. The peak concentration would be the dose into the specified volume.

Q. Sorry, so just -- if you give a higher dose you get a higher peak concentration?

MS. CHACON: Objection; mischaracterizes testimony.

A. Keeping the volume the same, yes.

Q. Okay.

A. Volume into which you're injecting it the same, yes.

Q. So in this context, species is a proxy for volume, right? Like humans have the same volume as each other and rabbits have the same volume as each other, generally speaking?

A. No, I'm not following your question at all.

But to your --to clarify your first question, if I put one six-pack of Coca-Cola in a refrigerator, that's a peak

concentration of six per refrigerator. If I put two six-packs, that's 12 con -- you know, that's 12 cans per refrigerator. So the peak concentration is effectively doubled.

If you'd like to repeat your last question, I'm happy to answer it.

Q. Sure.

You mentioned that concentration -- peak concentration also is a function of the volume into which you're injecting the drug, right?

A. Correct.

Q. Okay.

And do all humans have -- well, let's start with rabbits. I guess we're talking about rabbits.

Do all rabbits have the same intravitreal volume?

A. Same, of course not. We don't all have the same height measured with -- to microns.

But when you say "same," is an approximation. Different species. These were Dutch Belted rabbits. They have

approximately, I believe, it's 1.5 milligram -- milliliter volume in the vitreous cavity.

Q. Okay.

A. And that will change if the lens is removed because now there's nothing occupying that space, right, from.

Q. Okay.

And do all humans have the same intravitreal volume?

A. No. People with -- people's anatomy can differ. It's a range. People who are extremely farsighted typically have a very low vitreous volume, and people who are very nearsighted can have a high vitreous volume.

As an average, in aphakic, that is patient who has not undergone cataract surgery, we use approximately 4 or 4 1/2, but there are patients who can have a 9 mill -- 9 milliliter vitreous volume. And this is -- this is anatomic variation.

Q. Does anyone -- do any --

MS. KAYALI: Strike that.

Q. Does any group of people have a

smaller than normal vitreous volume?

A. I haven't studied it, but I would imagine the pygmies have a smaller than normal vitreous volume or --

Q. Sorry, what are pygmies?

A. The Asian -- African race with extremely short stature.

Pygmies, I think they're designated.

Q. Okay.

So, different humans can experience different peak concentrations using the same drug dose?

MS. CHACON: Objection; vague; calls for speculation.

A. I -- I don't understand.

Your -- every -- every single -- in terms of the definition that we've described, every single peak concentration would be different because no two humans have precisely the same vitreous volume measured to microliters.

Q. Okay.

And that -- do the differences in that peak concentration matter

sometimes?

A. No.

Q. Why not?

A. Well, in this particular -- in the context we're discussing of this drug, they did not matter. But there will be examples where they may matter. So you -- it would have to be studied on a person-by-person specific drug basis, and I -- I can't comment on everything.

Putting hot lead in the eye of any volume is apt to be extremely damaging.

Putting this drug at any volume was found to be not related to the peak concentration and everything in between.

Q. Sorry, putting this drug at any volume was not found to be related to --

A. No, putting this drug at any con -- at any con -- was related to peak concentration.

Let me rephrase.

Q. Please.

A. This study showed that the toxicities that were determined in prior

studies were preserved even in eyes that were altered surgically, that therefore underwent different peak concentrations, that underwent different elusions from the eye as they were injected.

Q. And I see. And so is that summarized in the -- I guess the last sentence of that bolded paragraph: These findings find that the mechanism of toxicity may be related to peak drug concentration rather than duration of tissue exposure?

A. For this drug, yes, precisely.

Q. Okay.

MS. KAYALI: Okay. We can turn to another document then.

This will be marked as 2043.

(D'Amico Exhibit 2043, Oum article, Graefe's Archive For Clinical and Experimental Ophthalmology 1992, was marked for identification, as of this date.)

BY MS. KAYALI:

Q. Dr. D'Amico, what is Exhibit 2043?

A. It's an experimental study that I did with Boo Sup Oum and Hyung Woo Kwak and others relating to intravitreal antibiotic therapy with vancomycin and aminoglycoside. This is a look after therapy is applied repetitively after the surgical alteration of the eye.

Q. Okay.

What did you conclude in this study?

A. That multiple in -- with these particular drugs, that after one injection, there was little evidence of change. After a second injection, there was more. And after a third -- I believe it did third injections. Let me review it here.

After a single -- after two or three sets of injections, I remember it well, that there was cumulative toxicity for this combination of agents.

Q. Okay.

So for a drug that's injected repeatedly, sometimes a single injection looked safe, but then multiple injections

turned out not to be safe?

MS. CHACON: Objection; vague.

A. This -- this was not a single. This was two drugs injected repetitively.

So, based on this study, I cannot comment on a single drug injected.

Q. That's a -- I -- you're talking about vancomycin and aminoglycoside?

A. Right.

And the reason this combination was chosen is this is the standard cocktail administered to patients who's had cataract surgery and develop an infection. So there was a need to understand would reinjecting such a patient cause harm. But this study makes no comments about single injection therapy.

Q. Sorry, okay.

So, I think the point -- the distinction you're making, hopefully I've got this right, is that in this study you're always talking about the combination of two drugs?

A. Correct.

Q. Okay.

And you were -- well, let's maybe can we turn to the "Discussion" section that's on page 59?

Okay. And you say: The present study documented that a single administration of a combination of vancomycin and aminoglycoside was well tolerated in the rabbit eye in the absence of lens and vitreous.

Did I read that right?

A. Yes.

Q. Okay.

And am I right in understanding that what you're saying is one injection of the combination, so --

MS. KAYALI: Sorry, let me strike that.

Q. If I say that, just for ease of reference, if I say "the study drug," will you understand that I mean vancomycin and aminoglycoside in combination?

A. Yes.

Q. So what you're saying is one injection --

MS. KAYALI: Strike.

Sorry, this is complicated for me.

Q. One intravitreal --

MS. KAYALI: Sorry, strike that.

Q. One injection of the intravitreal study drug looked safe in the rabbit eye, right?

MS. CHACON: Objection; mischaracterizes the document.

A. Yes, one injection of the combination therapy appeared to have minimal anatomic changes based on electron microscopy and fundus photography in the study eye.

Q. Okay. I said safe and you, honestly, said a lot more words that I'm not entirely sure I understand.

The discussion says: The study demonstrated that the study drug was well tolerated in the rabbit eye in a single injection.

Are you -- are you distinguishing between that and safety?

A. Yes.

Q. Why?
A. Well, well tolerated is in a -- this is an anatomical study. I have -- and also we used -- we looked at fundoscopy which is take -- looking at the eye, looking at the retina with a camera and in direct.
But "safety" to me is a -- would be -- imply a much bigger word than did the animal lose its ability to have children or a million other things that are not the subject of this study.
"Well tolerated" in an anatomical study is, to me, a much more limited term.
Q. Okay.
So well tolerated doesn't mean safe?
A. No.
Q. And in this instance, a single injection of the intravitreal study drug was well tolerated, but repetitive injections caused retinal toxicity, right?
A. Yes.
Q. So, for intravitreal drugs,

sometimes a single dose can, sort of, give a misleading signal of the overall safety of the repetitive dosing?

A. It would be depended on the study class of these drugs. These drugs are famous -- the whole reason that we were studying them is that they're famous for accumulation in tissues. Many drugs do not accumulate in tissues.

Your previous question referenced lysosomal accumulation. So these drugs were in -- in the literature to -- to scientific pharmacology were known to be drugs that accumulate in body tissues. So that's the reason for the study.

I would not, by any ways, characterize most drugs or even many drugs in that category.

Q. The tissues that they were sticking around in, for lack of a better word, one of them was the vitreous, right?

A. No. It was the retinal pigment epithelium and primarily -- and those were the subject of the electron micrographs in

the -- in the document.

Q. I see.

So there was, I don't understand all the pharmacokinetics, but the -- there was -- well, let me -- let me see if I can ask it this way.

Can you look at page 60? Repetitive -- I'm sorry, second paragraph. Do you see the word "repetitive"?

It says: Repetitive intravitreal injections have been considered in the past.

And then it goes on, and do you see the sentence beginning "Cobo and Forster"?

A. Yes.

Q. (Reading)...determined a half-life of 32 hours for intravitreal gentamicin and calculated that the optimal time for reinjection of intravitreal gentamicin would be 36 to 48 hours in aphakic eyes and 72 to 96 hours in phakic cases.

Do you see that?

A. Yes.

Q. What is a half-life?
A. So, a -- in pharmacology, we generally consider a half-life is like radiation half-life. If you start with a milligram of drug in the vitreous, given that all drugs are different, at what point will you have half a milligram left. And that may be four hours; it could be 34 hours. And that's considered a half-life. And that's done by repetitively dosing and studying things at very careful time points.
Q. Okay. It says that on the basis of half-life, the authors calculated that the optimal time for rejection of intravitreal gentamicin would be 36 to 48 hours in aphakic eyes and 72 to 96 hours in phakic cases.
Why is half-life important --
MS. KAYALI: Let me strike that.
Q. Why -- why did --
MS. KAYALI: Strike that.
Q. Why did Cobo and Forster use half-life to determine when to reinject?
MS. CHACON: Objection; calls

for speculation.

A. Because they were wrong. The whole point of the study is to show that -- normally when you do certain drug dosages, you base it on half-life. You say that, I'm giving you an antibiotic and I want you to take a pill morning and bedtime because other studies have shown that this will have a certain distribution in your body, et cetera, et cetera. And those distribution studies based on half-life drive certain dosing schedules.

However, there can be toxicities that occur even with a half-life calculation if the drug is accumulating in the various tissues in the body.

This is a drug that accumulates. The purpose of this study was to show that if you -- if you repetitively inject this drug, even though half-life calculations would have shown you that you might want to do it to sustain a level, you're going to get toxicity in the retinal pigment epithelium. So it's a disparity between one way of suggesting drug doses versus

another toxicity study, or in this case an anatomic study.

Q. Okay.

So, ordinarily a skilled person would consider half-life in estimating an appropriate, or maybe in forming an expectation about appropriate injection interval, but it might turn out to be informative or it might not?

MS. CHACON: Objection; vague; calls for speculation.

A. Yeah, it's highly speculative, in my opinion. But certainly knowledge of the -- the broad knowledge of half-life, of previous toxicity and related compounds, of dosing schedules, of species specific effects, of volume into which something -- it would be one of the many factors that would guide selection of dosing for an -- an agent.

Q. Okay.

So, important to consider when thinking about dosing interval, but not necessarily dictating dosing interval, right?

MS. CHACON: Objection; vague; calls for speculation.

A. Yes, in general, it would not be, to use your term, dispositive.

Q. But it would be important to consider?

MS. CHACON: Objection.

A. Not necessarily.

MS. CHACON: Hold on, Dr. D'Amico. Let me get my objections on the record.

Objection. Same objections.

Go ahead.

A. Not necessarily.

Certain agents are dosed one and therefore half-life is unimportant.

Q. Fair enough, okay.

So if you're contemplating multiple injections, you would always consider half-life, it just may not be dispositive?

MS. CHACON: Objection; vague. Same objections.

A. Again, it would depend on the route of administration. It might be

completely irrelevant to consider how often you put suntan lotion on your skin versus how often you're going to dose an antibiotic. So it would be very circumstance dependent.

Q. Okay. So -- sorry, that's very fair.

With respect to intravitreal drugs, in the context of this study we're talking about repetitive intravitreal injections, right?

A. Of antibiotics.

Q. Okay.

And when determining how frequently to dose an intravitreal drug, half-life is important to consider, but may not be dispositive?

MS. CHACON: Objection; asked and answered; vague.

A. It -- it may not, yes. I agree with that.

Q. But it's important to consider?

A. Define "important."

It's one of the many factors that it's -- it -- not necessarily the

most important factor at all. The efficacy of the drug, for example, would be an important factor, but the half-life would be somewhere on that list, but I'd have to know what you consider important.

It would be one of many factors that I would take into my consideration.

Q. But the skilled person would take into consideration when formulating dosing intervals?

MS. CHACON: Objection; asked and answered; calls for speculation.

A. Yes.

Q. Okay.

Sorry, can we go back to the Discussion for a sec? You said: The present study documented the single administration of a combination of vancomycin and aminoglycoside was well tolerated in the rabbit eye.

And I think you agreed that "well tolerated" is not the same thing as "safe."

MS. CHACON: Objection.

BY MS. KAYALI:

Q. Why?

MS. CHACON: Mischaracterizes testimony.

A. Are you asking -- you're asking me why "well tolerated" is -- 'cause I'm studying only one element, which is retinal -- the reason I do not consider "well tolerated" to be equal to "safety" is that I'm merely studying the anatomic appearance of the retina and the fundus appearance of the retina after intravitreal injection. There -- I didn't, for example, study the corneal endothelial cell count or the tear film thickness or a million other factors that could have been studied in this thing, so.

Q. Okay.

So you can't get an expectation or a reasonable expectation of safety from the fact that something is well tolerated?

MS. CHACON: Objection; calls for a legal conclusion; calls for speculation.

A. You said I can't.

If the answer is I do not think that "well tolerated" is equivalent to "safety," no. Yes, I do not think that "well tolerated" is equivalent to "safety."

I'm kind of getting wrapped up in your words here.

Q. Lots of double negatives in that one here.

A. Yes, lots.

Q. Let me try again.

I think we agree that just because something is well tolerated, that statement does not provide a reasonable expectation that it will be safe, right?

MS. CHACON: Objection; asked and answered; calls for legal conclusion.

A. Yeah, you'd have --

MS. CHACON: One second, Dr. D'Amico.

And calls for speculation.

Go ahead.

A. You would need to provide a precise definition of "safety" and -- for

that question. I cannot answer without speculating what you mean by "safety."

Q. Okay. Well, we just talked about -- you just agreed that "well tolerated" is not the same as "safe," right?

A. Right.

Q. So I'm talking about "safe" in the way you used it the last time we used the word "safe."

So, the -- the phrase "well tolerated" does not provide a reasonable expectation that something will be safe?

MS. CHACON: Objection; calls for legal conclusion; calls for speculation; asked and answered.

A. Yeah, that's too strong.

I said that it could be. It could be completely safe. I know nothing about the other elements that I've discussed, such as corneal endothelial cell count or lid function with tear film, et cetera. But certainly it's better that a drug is well tolerated on the pathway to a more comprehensive safety profile, but

it is not -- it is not an assurance that the drug will be completely safe.

Q. Okay.

It doesn't provide an expectation that the drug will be completely safe, right?

MS. CHACON: Objection; asked and answered; calls for legal conclusion; calls for speculation.

A. Again, now we're talking about expectations. The -- the study is very clear that it's an anatomic study of acute intervention time points after one, two, or three doses of a combination of an antibiotic therapy which is known to accumulate in tissues.

I cannot generalize from this to expectations of how other drugs would perform.

Q. Okay.

MS. KAYALI: Okay. Let's take a look at another document.

MS. CHACON: Well, and I would suggest, counsel, before you do, we just take a short break, just a bio

break, if that's okay?

MS. KAYALI: Would you like to take a break?

THE WITNESS: Sure.

MS. KAYALI: Okay.

THE VIDEOGRAPHER: The time right now is 10:55 a.m., and we're off the record.

(Recess taken.)

THE VIDEOGRAPHER: The time right now is 11:17 a.m., and we're back on the record.

MS. KAYALI: Welcome back, Dr. D'Amico.

BY MS. KAYALI:

Q. Did you, at any time during the break, discuss your testimony with counsel?

A. No.

MS. KAYALI: I'm going to hand you what will be marked as Exhibit 2044.

(D'Amico Exhibit 2044, Sakarya article European Journal Ophthalmology 2010, was marked for identification,

as of this date.)

BY MS. KAYALI:

Q. Do you recognize this document?

A. No.

Q. Feel free to take a moment to review it, but when you're ready, can you let me know what it is?

A. (Witness reads document.)

Q. And I apologize, Dr. D'Amico. I'm not trying to hurry you up. I just want to make sure you're not waiting for a question.

A. No, I am not waiting for a question. Thank you.

(Witness reads document.)

I have an initial familiarization with the study.

Q. Okay.

This study concerns cefuroxime, right?

A. Cefuroxime (different pronunciation).

Q. Okay.

What is cefuroxime?

A. It's an antibiotic.

Q. And what's the normal -- well, let me ask --

MS. KAYALI: Let me strike that.

Q. What kind of antibiotic is it?

A. I -- I don't know.

Q. Okay.

A. I think it -- it sounds like it's one of the newer recombinant cephalosporins. I believe that's what it is, a recombinant cephalosporin.

Yes, I'm sure that's what it is.

Q. Okay.

Do you know how it kills bacteria?

A. I do not.

Q. Okay.

What's the normal dose of intracameral cefuroxime as prophylaxis during cataract surgery?

MS. CHACON: Objection; foundation; calls for speculation.

A. This -- this paper asserts that that dose is 1 milligram, but I don't know if that's a normal dose or a dose, you know, for this particular clinic,

et cetera.

I do not, as I mentioned, perform cataract surgery.

Q. But you mentioned earlier that you've published on appropriate dosages of antibiotics as prophylaxis during cataract surgery, right?

A. Yes, but I've never studied or utilized cefuroxime.

Q. Okay.

Any reason to disagree with that 1 milligram per milliliter is the appropriate dose of cefuroxime?

A. With --

MS. CHACON: Objection; vague.

A. Without a review of all the available studies related to intravitreal cefuroxime, I have no basis to agree or disagree with the dose.

Q. Okay.

Have you ever published that the appropriate dose, or the standard dose maybe is a better word, of cefuroxime after cataract surgery is 1 milligram per milliliter?

A. I -- I'm not aware. I may have been a participant in a review article or something that mentioned it, but it is not a drug that I have ever personally administered to an eye.

Q. Okay.

But you have administered other antibiotics to an eye during cataract -- or, excuse me. During cataract surgery as prophylaxis for endophthalmitis?

A. No. As I mentioned, I do not perform cataract surgery. Therefore, I have never administered prophylactic antibiotics during cataract surgery.

Q. Well, earlier you said you'd performed it during residency and you had experience injecting intracameral antibiotics during your residency and when you did perform cataract surgery.

So where have we gone astray?

A. If I could ask the court reporter to read a statement where I said I'd injected intracameral antibiotics during cataract surgery, that would be helpful.

I said that I'd performed cataract surgery during my residency and that I had experience with intra -- intraocular antibiotics, but I don't recall -- I didn't perform -- I don't use intracameral antibiotics as a resident.

Q. Okay. So, you say: My CV indicates says articles in which I studied rabbit with intravitreal drug therapy.

And then I said: And there also -- there are also intracameral antibiotics in cataract surgery, right? And you studied those?

And you said: Correct.

And then you earlier said have -- I asked: Have you ever performed cataract surgery?

And you said: Yes, as a resident.

And I said: Do -- are antibiotics used prophylactically in cataract surgery?

And you said: They are.

And you said: And you've also had experience administering those, right?

And you say: I have experience. I also have extensive experience doing research on the subject that we're discussing.

That is prophylactic antibiotics at cataract surgery for the treatment or prevention of endophthalmitis.

Yes, I performed cataract surgery as a resident as all residents do, but subsequent to my specialization I do not perform conventional cataract surgery.

Then you go on.

A. Let me know when you'd like a response.

Q. Sure. Go ahead.

A. Topical drops are prophylactic antibiotics widely used for cataract surgery.

There's no mention of "intravitreal therapy" in the statement you just read.

We routinely give to every single patient prophylactic antibiotics. If you mention prophylactic antibiotics to an ophthalmologic surgeon, their first

response is going to be of course you're going to give topical drops. What about intravitreal intracameral surgery is a highly specialized procedure done by cataract surgeons.

Subsequent to the time period that we're discussing, I do not perform cataract surgery and have never administered intracameral antibiotics in association with cataract surgery.

So, my -- your statement was general and would certainly cover prophylactic antibiosis with - with topical drops.

Q. Okay.

So, this paper discussing a dilution error in the administration of cefuroxime mean intracamerally, right?

A. Yes.

MS. CHACON: Objection; foundation.

BY MS. KAYALI:

Q. And the -- the paper says that the normal dose is 1 mg per 0.1 milliliter, but in this study, the

investigator accidentally -- or, excuse me, the -- the surgeon accidentally administered 3 milligrams in 0.1 milliliters, right?

A. Yes.

Q. Okay.

Have you ever accidentally administered an overdose of a drug as an injection into the eye?

A. Not to my knowledge.

Q. Okay.

That's something you work hard to avoid, right?

A. Correct.

Q. Okay.

This paper says that the accidental overdose of three times the normal dosage was well tolerated. It didn't cause any detectable adverse effect, right?

MS. CHACON: Objection; mischaracterizes the reference.

A. Correct.

Q. Okay.

And so, on the basis of this

publication, the skilled person would have a reason next time to administer 3 milligrams instead of 1 milligram as antibiotic prophylaxis after cataract surgery, right?

MS. CHACON: Objection; calls for speculation; calls for --

A. No.

MS. CHACON: One moment, Dr. D'Amico.

It calls for a legal conclusion.

Go ahead.

A. Not at all. I completely disagree.

This is a one-week endpoint. We don't know how these patients did at two weeks or four weeks. They may have all gone blind.

So your supposition that this is a wonderful dose level is not -- there's no data available in this paper beyond one week.

Q. Okay. Do you see in the second paragraph in the right-hand column it says: The six patients were followed up

very closely every day during the first week. And then it goes -- it continues and the last sentence is. After the first week, patients were examined at one-week intervals for one month and all patients were followed up for six months at one month intervals. There was no significant change in ocular findings in this period.

So on the basis of that information, the skilled person would have a reason to administer 3 milligrams next time, 3 milligrams of cefuroxime next time, right?

MS. CHACON: Objection; calls for speculation --

A. Yeah, not --

MS. CHACON: -- legal conclusion.

A. Yeah, not necessarily. This is a prophylactic administration. So, prophylactic drugs are in a very different category than therapeutic drugs. They have to have a much higher level of safety because they are administered to a broad population. Every single patient who

undergoes cataract surgery in some clinics is subjected to these drugs, and if there was an overdose from one to three, indicating laxity on the part of the people making the dilution -- making the dilution or difficulty, then it could be three to nine the next time. And these are administered to thousands of patients.

So, I do not -- and I have spoken in my career about avoiding prophylactic therapy precisely because of the problem. It's more -- more likely, in my opinion, to result in overdosage and even potential toxicity, as we've seen with other agents, than to prevent a case of infection.

So, there are many elements of this that I disagree with. This would not urge me to do prophylactic therapy at all. It would say that prophylactic therapy is a time bomb waiting to go off in your clinic. These people happened to get lucky, but it's just one more reason to avoid administering this type of antibiosis to large groups of patients who

probably never need it.

The incidence of endophthalmitis is one in 1200 cases. Treating 1200 eyes perfectly with dilutions to prevent one case of endophthalmitis doesn't seem like a reasonable bargain to me.

Q. So, that's -- what you just said is a suggestion that you don't think there should be antibiotic prophylaxis in these incidences at all, not -- it's not about the dose, right?

MS. CHACON: Objection; mischaracterizes testimony.

A. No. I'm just saying that in my preference in the medical information available to me, I do not support widespread antibiotic prophylaxis on a normal population.

I do -- I do support the use of preoperative topical drops, and certainly in high-risk patients, patients with immunosuppression, chronic lid infections, surface abnormalities, those patients are good candidates for selective prophylaxis. However, blanket prophylaxis is more prone

to create dilution errors and under or overdosages than to be effective as prevention.

Q. Okay.

So, let's say we're talking about a patient where you do think antibiotic prophylaxis is appropriate. Okay. Are you with me?

A. Mm-hm.

Q. This publication provides an expectation that next time someone's administering intracameral cefuroxime, they have a reason to use 3 milligrams in 0.1 milliliters rather than 1 milligram in 0.1 milliliters, right?

MS. CHACON: Objection; calls for speculation, incomplete hypothetical.

A. I -- I don't know what I would do based on 3 milligrams.

We already know that the -- I would have -- I would need more confirmation that this is a clinic that obviously has issues with creating the dilutions, who made them, how did they

make them, et cetera. Do we really know that it was three. Do we really know that it was one.

This is a publication that would require confirmation for me to incorporate it in my practice patterns.

Q. Because it's only an isolated incident?

MS. CHACON: Objection; vague; calls for speculation.

A. Yes, and it doesn't provide details of who created the dilution. Was the dilution -- for example, the dilution could be made in the operating room by a nurse who's in a hurry, or it could have been made by a trained pharmacist.

Also, I'm unfamiliar with this clinic and these authors, et cetera.

So this is the kind of information that you would take into account, but you would certainly want confirmation before you would shift your practice pattern, or at least I would in this particular instance with an antibiotic that's being administered for a

presumptive need, not a real need. This is prophylactic therapy which is quite different than treating therapy.

Q. But this document shows that subsequent injections of intracameral cefuroxime at a dose of 3 milligrams in 0.1 milliliters will expected to be safe in additional patients, right?

MS. CHACON: Objection; vague --

A. Again, I --

MS. CHACON: -- calls for speculation.

A. Again, I disagree. There is -- to my knowledge, there is no approved agent for prophylactic therapy at cataract surgery up -- there may not even be one now. I haven't reviewed the field. But there is no specific approval because the treatment of these -- of these -- of prophylaxis at cataract surgery is optional. There is no disease present. This is a prophylactic therapy and therefore must be treated, because it's going to be given to a wide population, must be treated with special -- if you're

going to do it, it has to be a hundred percent safe. 1199 patients have to be treated safely to prevent that one case of endophthalmitis.

Q. Okay. Sorry. I think we're maybe talking past each other.

I want you to assume that you've decided a given patient does require intracameral antibiotic prophylaxis.

Okay. Are you with me?

A. Mm-hm.

Q. What I'm asking is based on this document, you would expect that you could instead of administering 1 milligram per 0.1 milliliter, it would be safe to administer 3 milligrams in 0.1 milliliter?

MS. CHACON: Objection.

BY MS. KAYALI:

Q. Do you agree or disagree with that?

A. I --

MS. CHACON: Objection; asked and answered; calls for speculation; incomplete hypothetical.

A. I disagree.

Q. Okay.

A. You are ignoring in your question the -- my evaluation of the quality of the data in this report. I would give this -- the data in this report very different credence to what I might give a -- a more rigorously conducted trial with, you know, multiple observations.

This is from a single clinic in -- in Turkey with authors unknown to me with incomplete information of who prepared this formulation and how sure were they of the 3 milligram dosage. Did they subsequently say that they analyzed the syringes that they used and there were 3 milligrams. That's something that we would do in -- in an overdose.

So we -- we -- this report, I would weight much less than the question would imply.

Q. You wouldn't give much credence to an isolated instance of an overdose of intracameral cefuroxime as suggesting a higher dose is safe.

Am I summarizing your opinion correctly?

MS. CHACON: Objection; mischaracterizes testimony; vague.

A. Not in the least.

I would not give characterization of an isolated report out of Turkey with incomplete details regarding a drug dosage as a method to suddenly change my medical practice concerning a drug that I have never used in the eye.

Q. You keep saying "out of Turkey."

What's the relevance of the fact that it comes from Turkey?

A. The fact that -- the fact that I'm not familiar with all of their standards for operating room safety, for their -- the competence and the training of the various physicians. They're all thing -- all elements that one would have to consider in determining surgical data and pharmacologic data.

Q. Okay.

And so I -- I think what you're

saying is that you just don't really trust what's written here. Is that right?

MS. CHACON: Objection; mischaracterizes testimony.

A. Again, I didn't say I didn't trust it. It's data. But the quality of the data is -- is assigned a value by how many publications reproduce this result, what is the quality of the people who've gone into it, how thorough is their documentation, what are their subsequent follow-up presentations regarding this, et cetera.

There's a whole bunch of things that a person of ordinary skill of the art would utilize in whether they would change their medical practice.

An isolated report with incomplete details on a drug I've never used in a -- in a procedure that I don't agree with, although as your question says there may be patients in whom I could be convinced to do it, would not convince me to change my dosing schedule for this antibiotic.

Q. Okay.

Okay. You can put that aside.

In your opinion, back in 20 -- May of 2018, would the skilled person have wanted to administer intravitreal injections more frequently or less frequently?

MS. CHACON: Objection; vague.

A. Define "frequently."

Q. Well, I just mean it as a relative term.

Would you rather inject drugs more often or less often in the intravitreal context?

A. In the absence of efficacy data, I can't fully answer that question because if you suddenly -- if there were at 2018 -- you asked me would I like, if there was a drug that was on the horizon that totally cured vision and brought everybody back to see the way they were 15, I would give that every day if -- if it had such a miraculous result.

However, with the available agents as of the date you specified in

2018, I would prefer to inject a patient less frequently.

Q. Okay.

How much less frequently?

A. I -- I have -- I can't -- give me some metrics regarding your question, please.

Q. Well, sure. Maybe let's start -- let's start with an anchoring point.

How often do -- let's say -- take a patient with AMD. How often do -- would a single patient with AMD receive intravitreal injections?

MS. CHACON: Objection; incomplete hypothetical.

A. Yeah, I mean, it varies. Some patients receive injections at -- in 2018 monthly. Some patients receive injections at intervals between one month and three months. And occasional patients receive an injection and never need another one.

So, but whatever the frequency, one would wish to give less injections. The frequency would depend on a given

patient, in other words.

Q. I see.

But you can tell ahead of time which patients are going to need more injections and which patients will need less, right?

A. No, I disagree.

Patients -- patient responses, as is documented in many elements that we've been discussing -- will discuss or have been discussing, patient responses are variable. Some patients have a quick response; some patients don't, to the same agent. So we cannot tell in advance -- I cannot predict in advance who will respond to therapy.

Q. Okay.

And can you predict in advance -- once you're working with a given patient, can you predict in advance how frequently they're going to need to be injected in order to respond to therapy?

A. No, I cannot predict in advance. Some patients will have plateau where they will be -- do very well and then fall off

the cliff and need more frequent. Some patients will go into what we could almost consider remission and go for years without needing another injection and everything in between.

Q. Well, why -- why is that? Do we have an understanding of why there's such variability?

A. I -- I certainly do not understand, but I presume it's due to biological effects and other elements of the -- of macular degeneration, diabetic retinopathy that have not yet been elucidated.

Q. So a given drug might be safe and effective in one patient but not another?

MS. CHACON: Objection; mischaracterizes testimony; calls for speculation.

A. Yeah, I mean, you've really -- forgive me, that question rolls a lot of stuff together. Safe and effective in one.

It is -- it is established fact

that a given drug does not always work for every patient even for the -- a given disease, whether we're describing cancer or psoriasis or any disease. There are -- there's patient variability in virtually every element of drug therapy.

Q. And the same is true for safety?

MS. CHACON: Objection; vague.

A. Again, yes, there's variation in safety for every patient.

For example, certain patients may be more prone to side effects if they have a certain genetic profile, and that is, again, established fact prior to the 2018 date that you described.

Q. What else other than genetic profile could make a drug unsafe in a person that --

MS. KAYALI: Well, that's a bad question.

Q. You mentioned genetic profiles as one factor that could affect safety.

What are some other factors?

A. That would be a lengthy discussion.

The -- the size of the patient. Dosage schedules are given typically milligram per kilogram of body weight very, very often. The sex of the patient could determine it. The -- the patient's other medications that they take. Additional conditions. Says every evening on TV "Do not take this if you have, you know, multiple endocrine neoplasia type 1 associated conditions." Allergies.

The list is rather lengthy.

Shall I continue?

Q. Well, I just want to make sure before you do continue that we're talking about intravitreal anti-VEGF agents right now, right?

A. I didn't hear "intravitreal anti-VEGF agents" in your question.

Q. Okay. Well, I -- we have been talking about how often -- whether or not you know how often patients are going to receive intravitreal anti-VEGF therapy, and I think you told me that you can't predict that ahead of time.

Now I'm asking are there

variability amongst individuals as to the safety of anti-VEGF agents?

A. Could -- could I hear your original question back to me? Like three -- two questions ago? I want to make sure. I'm not -- not following you.

Q. Okay. Can -- I'm just asking this question now.

A. Okay. Good.

Q. Can we stick with that question?

A. Yeah.

Q. Okay.

A. Because before I'm pretty sure your question was general.

Q. Okay. Well, if so, my mistake.

I'm asking now about anti-VEGF agents, okay?

A. Okay. Now go ahead.

Q. Is what you just said true for anti-VEGF agents?

MS. CHACON: Objection; vague.

A. I don't know. I -- I don't think we have -- anti-VEGF are relatively recent on the scene, a few decades. And we certainly have information that patient

responses are variable. We have not yet elucidated all of the -- all of the reasons why patients will have a variable response.

Q. And when you say "variable response," you're talking about efficacy and about safety?

A. I think so.

Q. Okay.

Okay. Sorry. So, going back to where we started. Patient -- let -- or maybe, let's -- let's start this way. Let's start fresh.

Patient comes in to see you with neovascular AMD. What do you do next?

A. Typically you're -- of course there's an examination. That examination would include various tests, conversation with the patient, explanation of the needs and risks and benefits of treatment and all of that for a patient with neovascular AMD, if the -- if there is evidence of wet AMD, and that would require a whole long discussion. But let's assume that we know what wet AMD is, I would typically offer

to initiate therapy with an anti-VEGF. I would explain to the patient that we don't know if this -- if you will respond, but studies suggest that there's a reasonable expectation of success with treatment.

I would go over the -- their fears undoubtedly and concerns about receiving an injection to the eye. I would allay those fears to the best I can.

I would indicate that there would be a follow-up examination probably with another injection in four to five weeks.

I would explain to the accompanying person the same things and ask if they have any questions.

I would perform sterile -- sterilization procedures to be able to administer the injection, give the injection, monitor the patient afterward to make sure they do not have any issues with just having had an injection, wash out the Betadine from their eye, describe postoperative instructions about what I would want to be called for, and

subsequently discharge the patient from my -- from my visit of that day.

Q. That's a lot.

You -- you said that you would explain to the patient about studies relating to the treatment.

What studies are you referring to?

A. That these are FDA-approved agents that we are administering you to. It's not something that I cooked up in a back kitchen, that I'm giving you an approved drug therapy that has been used in many patients and I think it's the best thing for your eye.

Q. Okay.

When you say "cooked up in a back kitchen," you're looking -- were you looking for our old cefuroxime exhibit?

A. I think so.

Q. Okay.

Where's the best place to go look for study results? Like, where as the skilled person do you find the information that you feel gives you the

comfort that this treatment is the best thing for the patient's eye?

A. There's -- there's no one place. Your question implies that there's a best place. You know, I do not see it as a best place.

I include written articles, presentations at meetings, conversations on chair lifts, discussions with colleagues. There's a whole host of informational sources that I utilize to make my clinical decisions, and I value them according, in my own personal strengths and weaknesses, as to how I evaluate the strength of the data in front of me. But it's a vast array of inputs, and I wish to keep those as open, as expansive as possible.

Q. Okay.

Is the -- you've participated in clinical studies before --

A. Yes.

Q. -- as an investigator.

Have you written papers describing the results of clinical

studies?
A. Yes.
Q. Is that one source of the data that supports your understanding about whether these drugs are going to be safe and effective in patients?
A. Yes. Clinical studies are one source of data stream that I utilize.
Q. Okay.
And where would you go to obtain the clinical study information?
Excuse me. Where would you go to obtain the clinical study results?
A. Are you asking me where physically I would go?
Q. Or --
A. I would probably go to my study and look on the computer, if that's what -- but I would also call colleagues. I would also participate in meetings and pay attention to presentations. I would also search the Web for available information relating to areas that I wish to further educate myself.
Q. Maybe let me just ask a simpler

question.

When a new study in an anti-VEGF agent is published by the investigators, do you typically read that paper?

A. Yes.

Q. Okay.

And that paper is going to contain data showing the results of the clinical studies, right?

A. You say "that paper." There -- for a important trial, there are usually multiple papers. There's usually -- there are usually presentations prior to the study that describe the rationale for the study, the baseline characteristics that will be included, maybe even study design. Then there may be a presentation of preliminary results. Then there may be a presentation of one-year results. Then there -- often there's a pre-presentation of safety results. Then there may be a two-year and a five-year results.

So, the characterization of "that paper" is certainly something that I would take to be plural in -- in nature.

There are much data regarding -- and again, that is something that would figure into my assessment of credibility of the data because it's been, you know, documented and carefully curated over multiple years and -- and presented in multiple fora.

Q. Okay.

So if a study has multiple papers presenting its results, you would typically, in your capacity as a physician now, but as a hypothetical skilled person back in 2018, you would look at all of those papers, right?

A. You're -- you're trivializing them.

I think the multiple -- the multiple is -- is a feature of large studies that have so much data they can't really be presented in a single paper in editorial format. So "multiple" is something that does not inherently create the authority that I attribute to it. It's more the data, but they typically occur in multiple formats.

Q. I see.

So, is that -- I'm trying to see if we're on the same page.

All the data from the study is important. It might be published in a smaller study in one paper or it might be published in more papers if it's a bigger study?

A. Correct.

Q. Okay.

Do you prefer the primary pub -- investigator's publication to a review article?

MS. CHACON: Objection; vague.

A. Yeah, I mean, it -- it's completely arbitrary, the question. A -- a superb one or the other will obviously be better than a crummy other or one. So, I mean, asking -- you know, it's -- in my -- my mental bin, it's like saying do you prefer a great corner Italian neighborhood versus a totally disappointing Michelin star restaurant. It's -- it's a completely speculative preferential question, and I can't really

answer it.

Q. Okay.

Do review articles always include all the data and results of the clinical trials they summarize?

MS. CHACON: Objection; calls for speculation.

A. Again, I have not read all review articles and can't comment on what they always or never include, but they typically, in order to pass review, will include the major body of information regarding a given subject. There are always more articles available that a reviewer cannot include.

Q. Okay.

In your evaluation of a particular anti-VEGF agent, do you go look at the data as a clinician -- or, excuse me, as a -- as a skilled person, or do you just read other people's summaries of the data?

MS. CHACON: Objection; calls for speculation.

A. Yeah, I don't -- I don't

understand the "or" in that question.

You're asking me am I shutting myself off from one data stream in preference of another. I -- I will read the data. I will read comments about the data. I will ask colleagues about the data. I will listen to presentations. I will go to debates about the data. So it is not an either/or comment with one having a clear preference.

Q. So more information the better?

A. Yes.

Q. Okay.

Okay. So, we were -- we got here because we were talking about how you would treat an AMD patient, right, and you said you would probably recommend that the patient begin treatment with an anti-VEGF agent, right?

A. Yes.

Q. What would you explain to the patient, recognizing that there's going to be variability, what would you tell them to expect about how often they're going to get injections?

A. I would say that at the beginning, we will probably give several injections almost, assuming you don't have -- speaking to the patient, assuming you don't have problems with the injection and an infection detachment, something really rare, that you would probably get three or more injections on a four- or five-week basis as routine, and then after that we'll see.

And then I explain to them that some patients really stay with that timing. Some patients may be able to have periods of less; some may even need more. But generally, that's what I tell a patient, that I cannot predict, based on what I see today, which of those buckets you're going to be in.

Q. Okay.

So, these drugs are administered at most once every month and sometimes less than that, right?

MS. CHACON: Objection; vague.

A. Yeah. No, there are -- there are practitioners who will -- I've seen

presentations where certain practitioners will interleaf different agents. So for example to be specific, aflibercept and ranibizumab or ranibizumab and Avastin off-label at intervals more frequent than once per month, to try to do every two weeks. I have never personally done that, but it is something that people have done.

So your statement that limiting it to one month or -- or more or however it was originally phrased is inaccurate.

Q. Okay. Well, I guess what I'm driving at is a lot of your opinions in your declaration seem to be based on the premise that the skilled person would have wanted a drug that could be injected less frequently, and what I'm struggling with is -- is why this isn't good enough.

I mean, there are people injecting themselves with GLP-1s every week.

Why isn't monthly or biweekly good enough?

A. Oh, the -- the -- we actually have a word for it. We call it treatment

burden. It's not treatment joy. It's treatment burden.

These are patients who are elderly, who have to -- who are terrified of going blind, but often their main concern is taking their son-in-law out of work to drive them to, you know, Upper East Side Manhattan to sit in my waiting room and get an injection procedure. If that something could go from eight to ten times a year down to four or five times a year, that's a whole lot of joy in -- in -- in that patient family, and that would be an improvement.

Q. How much reduction in treatment burden would the POSA have wanted to achieve in May 2018?

MS. CHACON: Objection; vague.

A. Yeah, I -- it's a -- we wanted less -- we wanted an improvement in treatment burden and we wanted an improvement in efficacy. We wanted better care for our patients.

Q. You'd wanted that for a while, right, by May of 2018?

A. Yeah. It's clear that we were very interested in studying and ex -- exploring methods to improve both the efficacy and the duration of our therapy with anti-VEGF agents intravitreally.

Q. Were you aware that companies were trying to do so?

A. Yes.

Q. Which ones?

A. Regeneron was trying to do so and also Genentech.

Q. What about was there a drug called Abicibar [sic]?

A. Abicipar.

Q. Abicipar, thank you.

Who makes that one?

A. Not Novartis. I've forgotten. I've forgotten.

It's a DARPin compound. That much I recall.

Was it Allergan? I -- again, I don't know.

Q. Okay. Fair enough.

A. It was a major manufacturer.

Q. So that was a major manufacturer

trying to make an anti-VEGF agent, right?
A. Yes.
Q. And that the goal was to make a longer-lasting anti-VEGF agent that reduced treatment burden, right?
A. Yes.
Q. Okay.
And that failed, right? Abicipar's not on the market?
MS. CHACON: Objection; calls for speculation.
A. Those are different -- those are different things.
Abicipar did not fail. Abicipar was able to reduce the leakage and exudation in macular degeneration lesions. It was not a marketable drug. So, its efficacy was there, but it was not a marketable -- marketable drug because it caused inflammation. So as a result, it was not approved for release. But in terms of efficacy, the drug clearly dep -- demonstrated efficacy against age-related macular degeneration lesions. So the kind of characterization as failure is

incorrect.

Q. Okay.

If you think about the manufacturer, whoever it was, and their goal of creating for patients a longer-lasting anti-VEGF agent, that was ultimately unsuccessful, right?

MS. CHACON: Objection; asked and answered.

A. Yeah, I -- no. The -- we don't know that if they were -- for example, that compound had a PEGylated addition to it. Maybe it was the PEGylated addition that caused the inflammation. Maybe they can go back to the lab and remove that and have a drug that is better than sliced bread. We don't know from the available data.

But looking at it through the success of marketing and calling the science a failure I think is shortsighted.

Q. Okay. Let me maybe just ask a more black-and-white question then.

That drug did not succeed commercially, right?

A. Correct.
Q. And it was not approved by FDA?
A. Correct.
Q. Okay.
Do you know whether its duration was longer or shorter than existing anti-VEGF agents at the time?
A. I don't recall.
Q. Okay.
You also mentioned Genentech as an entity that was trying to make a longer-lasting VEGF agent, right?
A. Yes.
Q. Did they ultimately bring to market a longer-lasting VEGF agent?
A. No.
Q. Okay.
A. And I would recharacterize -- certainly that was -- the original statement of mine was true, but they were looking, of course, for additional efficacy in their -- in their trials.
Q. Okay.
So, circling back to where I started, like, GLP-1s seem to have taken

over the world lately. Those are typically en masse used to control weight, right?

MS. CHACON: Object.

A. I believe so. I'm not a -- an internist.

Q. Okay.

And patients are willing to inject themselves every week to manage their weight, but they wouldn't be willing to get injections every month to keep their eyesight?

MS. CHACON: Objection --

A. I don't under --

MS. CHACON: -- vague.

A. Yeah, I don't understand your question or its relevance to my expertise.

Q. Well, what I'm trying to understand is why when so many other drugs are administered much more frequently than anti-VEGF agents you still believe anti-VEGF agents as of May 2018 represented a substantial treatment burden.

A. Are you asking me to compare

a -- a younger patient giving an injection in the privacy of their own home on a daily basis with someone who requires someone to drive them into a physician's office and undergo multiple tests prior to receiving a procedure into the eye in a waiting room? Are you asking me to say why those are comparable?

I do not think they are in any way comparable at all, and therefore the question to me is -- is unanswerable.

Q. Okay.

Can you not -- is there not a way to make anti-VEGF agents injectable at home?

MS. CHACON: Objection; calls for speculation.

A. I think that -- that is a -- at this point, is a science fiction question, and as a trained vitreoretinal surgeon, I would not attempt it.

I cannot imagine an elderly patient with limited visual acuity attempting such a procedure.

Q. So, GLP-1s are injected under

the skin, right, instead of into the eye?
A. Correct.
Q. Okay.
And that's -- that has different requirements than injections that go into the eye?
MS. CHACON: Objection; calls for speculation.
MS. KAYALI: Let me ask a better question.
BY MS. KAYALI:
Q. The drugs that get injected under the skin have different properties than the drugs that can be injected into your eye, right?
MS. CHACON: Objection; calls for speculation; incomplete hypothetical.
A. Yeah, what do you mean by "different properties"? Now you're talking -- you're talking about properties of the drug. We were talking about route of injection.
A subcutaneous injection has been performed for decades for insulin,

for example, and is a common procedure that is widely accepted. Now it's been super -- that even, of course, had a strong motivation to reduce the injection frequency, and now we have devices that utilize that.

So I think it's clear that the -- the retina community prior to 2018, and even at the inception of anti-VEGF therapy, was very, very eager to improve both efficacy and the original duration of the results. So that was the motivation for it, and it -- indeed, it was borne out in the performance of trials by both Regeneron and also by Genentech to explore those with -- with different -- different doses.

Q. Okay. Maybe I'm -- maybe I'm just -- we may be talking past each other, and that's probably my fault.

A drug formulation that can be injected under your skin, subcutaneously, can that same formulation be injected intravitreally?

MS. CHACON: Objection; calls

for speculation; incomplete hypothetical.

A. Yeah, that's vague.

If it's -- if it's saline solution, I think the answer would be yes. If it's something else, you would have to provide specifics.

Many of the principles will be the same. Many of the principles will be the same, you know, stability on a shelf and loads of things, sterility, but there might be other properties that are different depending on the different environment for which the drug is used.

So without -- without providing specifics, I can't possibly answer the word "same".

Q. Okay. Well, let's maybe break it down then.

Are all the ingredients that -- inactive ingredients that can be put in a subcutaneous formulation, are all of those safe for intravitreal use?

MS. CHACON: Objection; vague; incomplete hypothetical.

A. Yeah, I mean, you're -- there -- there probably are some that we don't use in the eye. There are probably some that are present in the formulation but we filter out. There are probably some that are equally used.

So again, the question is -- is incredibly vague and would be -- you would have to provide specific examples of your formulation to know whether it could be used subcutaneously and also in the eye.

Q. Okay.

And if you looked at a given formulation of a subcutaneous drug, would you be able to determine that it could be safely injected to the eye?

MS. CHACON: Well --

A. If I looked at it?

MS. CHACON: One second, Doctor.

THE WITNESS: Sure.

MS. CHACON: Objection; calls for speculation; outside scope of the report.

A. Yeah, you're talking about looking at it. Drug safety studies are

not done by looking at the drug. There would be preliminary animal studies. There would be toxicity data. There would be all sorts of studies prior to predicting.

I am not a -- I'm not a drug designer, so I would not be able to predict based on -- nor would I think anyone -- nor would anyone use a drug that didn't go through the cascade of studies that I've just outlined.

Q. Okay. And I -- I may have created the wrong impression. When I say "look at a formulation" I'm not talking about, like, looking at the liquid in -- in the vial.

I'm asking if you saw the list of ingredients in a formulation, would you, a clinician, be able to determine whether those ingredients were safe for injection into the eye?

A. No.

MS. CHACON: Same objection.

A. No, I would not.

Q. Okay.

You'd have to rely on a formulation scientist for that, right?

A. And all other studies that I described.

Again, determination of safety in the eye in the way that we have -- I have broadly defined "safety," which I believe is the correct term, requires a host of information, one of which is knowing the background of all the ingredients. Number two is evaluating the studies that have been done in animals treating the target tissues and subsequently pilot clinical data followed by, ultimately, large-scale trials and including aftermarket studies that often will pick up toxicities or other adverse effects or even positive effects that we didn't see in the clinical trials.

Q. Okay.

I assume for this case you must have done some research about which ingredients are safe to use in intravitreal drugs though, right?

A. I worked in concert with

Dr. Falconer, and I have no particular expertise in drug formulation.

Q. Okay.

Have you ever been responsible for choosing the ingredients that go into the formulation of a drug?

A. No.

Q. Okay.

Walk me through how you do the injection, so let's say, like, from the time you walk into the room to right up to the time you put the needle in the eye.

When you walk into the room, is the syringe already prepared, or do you have to make it up?

A. It depends on the agent that I'm using. Some are available as a prefilled syringe and some are present as a vial.

Q. Do you personally do the preparation of the syringe?

A. Yes.

Q. And is that to prevent overdoses like the kinds we discussed earlier?

A. It's to do everything properly. It's -- that is one of the elements that

is part of why I personally draw up the vial.

Q. Okay.

Once you've drawn up the vial and you have the medication, or maybe even before that. When you're looking at the vial and you have the medication, do you examine the medication in the vial visually?

A. Yes. I'm aware that -- and we're speaking now of the subset that are not prefilled. So we have a prefill subset that I've already mentioned, but the non-prefill which still exists for certain agents, the vial, we would make sure that the vial came in the proper packaging and that I have the appropriate sterile draw-up needle, filter needle, that is used, that proper sterile technique is being employed, that I am able to get the appropriate amount of liquid drawn up, which is a bit of technique, but you have to make sure. You -- some of the vials contain excess. Some of the vials just give you barely

enough to get the right dose, and that's variable.

And so all of those things go into a physician drawing up an agent from a sterile vial as a basic part of our training.

Q. Okay.

And now I want you to think about looking at the drug in the vial and looking at the drug in the syringe.

Are you -- does the liquid in the vial or the syringe ever look wrong, for lack of a better word, to you?

A. I have never had that experience.

Q. What --

A. With the FDA-approved agents.

Q. What -- what might you be looking for when you're analyzing the normalness of a drug that you're about to inject?

A. That it's there, that the vial isn't cracked or broken in some way, that it didn't leak out and I have one that I want to tell the manufacturer you owe me,

you know, 18 hundred dollars or whatever because this vial was damaged in shipping.

Q. Okay.

What about the transparency or cloudiness of the liquid, have you ever observed precipitants or particles in the liquid?

A. No.

Q. Okay.

Is that something that would be concerning if you saw?

A. It's a filtered needle. If the manufacturer had provided information that the slight turbidity can be tolerate but make sure you use a filtered needle, I would go along with those FDA-approved instructions.

To my knowledge, none of the agents that I use have such a concern.

Q. Okay.

Do you know what protein aggregation is?

A. Yes.

Q. What is it?

A. Protein aggregation is the

clumping of proteins in a solution of any solute, solvent.

Q. What's the clinical effect of protein aggregation in anti-VEGF agents?

MS. CHACON: Objection; vague.

A. Yeah, it could range -- I -- I -- this is complete speculation on my part. It could range from completely irrelevant to important based on the characteristics.

The protein aggregates may simply be a settling issue in the vial that has nothing to do with its efficacy. It could be something that is filtered out. It could be something that the body breaks down in the eye and that gives prolonged efficacy.

All of those are unknown to me, again, but it is not an a priori harmful thing unless it would render the drug uninjectable and unsafe.

Q. Why would injecting aggregates potentially make a drug unsafe?

MS. CHACON: Objection; calls for speculation; incomplete

hypothetical.

A. Yeah, I don't -- I don't know anything regarding injecting aggregates.

Again, every preparation that I utilize is either a prefilled syringe which has been screened for particulates or a -- is a filtered needle.

The con -- the contents and protein aggregates in anything I have ever used is unknown to me.

Q. Okay.

Are you familiar with the term "stability"?

A. Yes.

Q. Does stability connect to protein aggregates, or outside -- is that outside your area?

MS. CHACON: Objection; vague.

A. That is fully outside my area of expertise.

Q. Fair enough.

As a clinician, do you have an understanding of whether there can be negative safety effects from injecting a solution with part -- containing

particulates into the eye?

MS. CHACON: Objection; calls for speculation.

A. Please repeat the question.

Q. Of course.

As a clinician, do you have an understanding of whether or not there can be negative effects on vision when you inject -- if you were to inject a drug formulation containing particulates?

MS. CHACON: Same objection.

BY MS. KAYALI:

Q. Into the eye?

MS. CHACON: Same objection.

A. No, what do you mean by "particulates" now? What are you describing --

Q. Well, I --

A. We've gone from protein aggregates to particulates, so I need a new definition.

Q. Are protein aggregates sometimes considered particulates, or do you not know?

A. I have no idea.

Q. Okay.

Are impurities sometimes considered particulates?

A. I have no idea.

Q. Okay.

Do you have any understanding of the USP guidelines for the amount or concentration of particulates that are permissible in an intravitreal drug?

A. Clearly not.

Q. Okay.

Do you have any understanding of whether those requirements are different for -- let me ask a better question.

Do you have under -- any understanding of whether the requirements for particulates in intravitreal drugs are different than the requirements for particulates in subcutaneous or intravenous or intramuscular drugs?

A. I do not have that information.

Q. Okay.

Are you familiar with any literature about what happens if you accidentally inject, like, an impure

solution into someone's eye?

MS. CHACON: Objection; vague.

A. Yeah, describe "impure solution."

Are you talking about one that's bacterially contaminated? Are you --

Q. Yeah, that's a fair -- that's a fair distinction.

I'm not talking about infection risk. I'm just talking about an injection, let's say, that contains sediment of some kind, particle, protein aggregate, whatever it is, that is not filtered out and gets injected into the patient's eye.

Is there literature explaining what happens?

A. Not that I'm aware of. I am aware of many cases of contaminated solutions that have been injected in the eye causing infections. I'm aware of cases of dosage and dilution error, et cetera. But I'm not aware of any article or body of science that -- that is known to me as a clinician that expresses

particulate problems with intravitreal injections.

Q. Okay.

And same goes for protein aggregates?

A. Yes.

Q. Are you aware of literature regarding antidrug antibodies pertaining to anti-VEGF agents?

A. I'm only vaguely aware of antidrug antibodies. They've been mentioned at -- obliquely, but do not, in my mind, seem to be an important subject.

Q. Okay.

A. From a clinical point of view.

Q. That was not anti -- let me ask a better question.

Antidrug antibodies, that was not a body of literature you thought was necessary to consider in forming your opinions in this case?

A. You're speaking -- excuse me. You're speaking about antibodies to an anti-VEGF agent?

Q. Yes. Yes, that's right.

A. Yes. No, I did not.

I'm aware of the field, but it's not a major -- in other words, unless they are demonstrated to be highly harmful to the patient and unless they are demonstrated to be a cause of either worsened efficacy, less duration, or in -- decreased safety, they are of less concern to me.

Q. Okay.

So you didn't consider literature concerning antidrug antibodies in forming your opinions expressed in your declaration, right?

A. Not to my knowledge.

Q. Okay.

Okay. What -- how do you decide which agent to inject the patient with?

A. In the United States, it's a complicated process because varying insurance carriers will have different approvals, and in some patients will have no approval for any agent and they would only be a candidate for, for example, off-label Avastin, which I rarely use, but

it -- that is a possibility.

Then the choice becomes between either aflibercept, ranibizumab, or faricimab. Ranibizumab is now less commonly used because the other two agents I mentioned appear to have longer duration and perhaps even higher efficacy.

The choice between faricimab and Eylea is kind of vague. It will depend on many circumstances, the patient's ability to qualify for insurance approval. Some insurance companies require longer with one agent than another. Depending on the disease. Until recently, certain diseases were only available for certain -- certain agents, et cetera. So it's complicated.

And stocking. We may go and say we want to give faricimab to this patient, but we only have, you know, ranibizumab in stock or we only have -- so there's loads of factors that go into that decision.

Q. Okay.

How do you decide what dose of the drug you should use?

A. Well, there -- it's based on the

FDA-approved products that are available in my refrigerator, and those are basically many: Faricimab, Eylea, Eylea HD, ranibizumab 0.5, ranibizumab 0.3, and off-label Avastin.

Q. What was the first one you said? I'm sorry?

A. Faricimab.

Q. And do you inject Beovu?

A. No.

Q. Why not?

A. Beovu was a -- was a highly efficacious compound that again had isolated but devastating instances of severe inflammation and even with retinal vasculitis and retinal necrosis. It is still available on the market, but I am one of the vast majority of retinal physicians who are too afraid to use it because -- and, you know, it -- that's a -- that's a widely held view, why with other agents available would you take a chance on losing the eye by injecting Beovu.

Q. So you don't view Beovu as a

successful drug?

A. I think the target that it targeted and its advantage of low molecular size was certainly of interest to us. So from a scientific point, there's new information available. But, no, it is not a successful product, using the word "product" as opposed to "drug."

Q. Okay.

So you follow the FDA-recommended dose for each of the various agents you just described, right?

A. Yes.

Q. Okay.

What about the volume of the injection, what's your preferred injection volume?

MS. CHACON: Objection; vague.

A. Well, preferred. The agents that I use have a prescribed injection volume, whether it's a prefill syringe to express to a marking line or whether it's a vial with a -- a dose volume specified in the -- in the packaging. So those are my preferred uses for those agents.

Q. Do you have a general preference for bigger or smaller injection volumes?

MS. CHACON: Objection; vague; calls for speculation.

A. You're -- you're asking me in general now. We're not speaking only of anti-VEGF, is that correct, or what?

Q. Let's take a intravitreal anti-VEGF agent. All things being equal, would you rather inject 50 microliters or 100 microliters?

A. I'd rather inject 50 microliters in that case.

Q. Okay.

Would you rather inject 50 microliters or 60 microliters?

A. 50 microliters.

Q. And why is that?

A. Because the -- the concerns on the low end are we would want to inject the smallest feasible volume in which we can actually deliver the medication through a 30-gauge needle and have a concentration that is stable on the shelf and meets all the other many requirements

for drug formulation. But the concern of volume is that as the volume of the injectate increases, then you have a chance that you will have high intraocular pressure, and that can cause elevation to a level that the central retinal artery is shut off and you are baby-sitting with the patient for a number of minutes until that pressure comes down. In some cases, it's not coming down fast enough and you even have to withdraw fluid from the eye in order to rescue the patient from the profound intraocular pressure.

So the number -- the lower the injection volume, the less chance you will have of that. It even occurs occasionally at patients with -- with 50 microliters injection, as every clinician knows, but in general, you would want a lower -- a lower vitreous volume injected.

Q. Okay.

And what you just described to me is what the skilled person would have understood as of May 2018, right?

A. Yes.

Q. Okay.

Is concentration the same thing as volume?

A. Not in the least.

Q. Are the concepts related?

A. Well, concentration is typically expressed over some unit of space, yes, or volume.

But yeah, I mean, it's same as miles per gallon or something. I mean, it's a related -- it can be a related concept.

Q. Okay.

So, if you change the volume of a formulation and keep the dose the same, you're adjusting the concentration, right?

A. Correct.

Q. Okay.

And conversely, if you change the dose of a formulation but you keep the volume the same, you've also changed the concentration, right?

A. If you -- say that again.

Q. Sure.

If you adjust the dose of a

formulation but you keep the volume the same, you've also adjusted the concentration, right?

A. Correct.

Q. Okay.

So concentration, volume, and dose, all three of those are related?

A. Yes.

Q. Okay.

What's the maximum protein concentration you can use in an intravitreal injection as of May 2018?

MS. CHACON: Objection; vague; calls for speculation.

A. I have no idea.

Q. Okay.

So you don't have an opinion as to what the skilled person would have wanted to achieve in terms of protein concentration for an intravitreal protein formulation as of May 2018, right?

A. I don't -- I don't think in terms of proteins, I'm sorry. I don't have a -- protein concentration is not on my daily list of variables that I think

of. I have no information regarding it.

Q. Okay.

And so not to be too formal, but this is just for the record, that means you didn't express any opinions in this case about what the appropriate concentration of a protein in formulation should be, right?

A. I -- I'd have to refresh my memory by reviewing the declaration.

Can you -- can I do so?

Q. You -- you're welcome to, but maybe we can short-circuit this.

I think you just said that you have no idea what the maximum protein concentration you can use in intravitreal injection as of May '18 would be, and I'm just asking whether you offered any opinions about things you have no idea about.

A. I don't recall. I -- I -- it's not my habit to offer things I have no opinion about, but this may be one at the my -- at the limits of my professional and chemical knowledge. So I would have to

see my document to make a full -- a firm statement.

Q. To find out whether you did offer an opinion about something you've just said you know nothing about?

A. Correct.

Q. Okay.

Did you tell Dr. Falconer what -- what concentration of protein he should use as a skilled person formulating an intravitreal aflibercept formulation?

MS. CHACON: Objection; vague.

A. Yeah. Again, I would need to -- to refresh my memory by reviewing my declaration. I don't recall out of hand if I spoke in terms of protein or in terms of volume to Dr. Falconer.

Q. Okay.

I reviewed your declaration. I don't see anywhere that you say what you told Dr. Falconer. So I realize you would have to read the whole thing to -- to know whether or not you do say what you told Dr. Falconer, but I just want you to assume for now that the declaration

doesn't say what the content of your conversation with Dr. Falconer was.

Do you understand what I'm saying?

A. Say that again.

Q. Sure.

I read your declaration front to back and I haven't found a place where you say, Here's what I told Dr. Falconer, okay.

And so you're obviously welcome to review your declaration, but I'm just asking for your memory at the moment.

Do you recall telling Dr. Falconer, You should put this concentration of aflibercept, or maybe better said, The skilled person would have wanted this concentration of aflibercept in an intravitreal protein formulation?

A. And may I --

MS. CHACON: Objection; vague.

A. I find the question -- I'd like to refer to my declaration where I describe a person of skill in the art.

May I do so?

Q. Sure. And I can help you with the paragraph, if you'd like.

A. It's --

Q. It's around --

A. -- legal -- it's legal some things here.

Where is the person of skilled --

Q. I think you want to get to paragraph 89, 90-ish.

A. All right. Let's try there.

Here -- here we go. Paragraph 90: A person of ordinary skill in the art (POSA) at the time of the invention would have been a multidisciplinary team that included a medical doctor in ophthalmology or a similar field with knowledge of angiogenic eye disorders including treatment and dosing regimens of drugs for intravitreal injection, including anti-VEGF drugs, at least several years conducting research on anti-VEGF treatments for angiogenic eye disorders and familiarity with the pharmacological properties of anti-VEGF treatments.

And, number 2, a Ph.D. in pharmaceutical sciences or a similar field with at least several years of experience in the development, manufacture, and characterization of therapeutic proteins, including, for example, fusion proteins or antibodies.

And then other individuals.

So, the question of what I told a person of ordinary skill of the art, it's clear that this was a multidisciplinary team, and I do not understand the need, having defined my -- the person of ordinary skill of the art as a multidisciplinary team, the fact that who told what to whom is -- is a relevant question.

Q. Okay. Well, let's maybe take a step back.

You have the -- in your opinion, do you have the qualifications of part 1 of the POSA set forth in paragraph 90?

A. Yes.

Q. Okay.

In your opinion, do you have the

qualifications set forth in paragraph 2 -- excuse me, in part 2 of paragraph 90?

A. As an individual, no.

Q. Okay.

And so when you say in paragraph 91: At the relevant time of the '036 patent conveyed to me by counsel, which is May 2018, I was at least a person of ordinary skill in the art by virtue of my clinical background.

Right?

A. Correct.

Q. Okay.

But you were only part of the person of ordinary skill in the art, right? You were the clinician part, not the formulator part?

MS. CHACON: Objection; calls for a legal conclusion.

A. Yeah, I've already defined what a person of ordinary skill in the art as set forth in my declaration and have read it in near full the first portion of the paragraph.

So the question to me is trying

to break down what part of a POSA is when I've already provided a definition seems -- seems not -- not appropriate, in my opinion.

Q. Okay.

Well, my question is you say in paragraph 91: I was at least a person of ordinary skill in the art by virtue of my clinical background.

Am I to understand by that that you mean you possess all the qualifications set forth in paragraph 90?

A. As a person of ordinary skill in the art as part of a multi -- would have been a multidisciplinary team, yes. I -- I participated in that, but I am -- the person of ordinary skill in the art, which is the relevant definition here, includes a multidisciplinary team.

Q. Okay.

So it's your testimony that you were at least a person of ordinary skill in the art who could have participated in a multidisciplinary team, but you do not have all the skills set forth in paragraph

95?

MS. CHACON: Objection; mischaracterizes testimony.

A. Yeah, you're -- you're -- Donald D'Amico does not have personally all of the skills, but Donald D'Amico as a person of ordinary skill in the art defined as it's set forth in paragraph 90 does possess those skills.

Q. So you, in forming your opinions, imputed to yourself the skills of a formulator?

A. No.

Q. So then help me understand.

A. It -- I'm part of a multidisciplinary team with access to the expertise of a formulator.

Q. Okay.

So you, without the formulator -- let's try this again.

Donald D'Amico, without access to a formulator, would not be at least a person of ordinary skill in the art?

MS. CHACON: Objection.

BY MS. KAYALI:

Q. However, you -- Donald D'Amico, who does have access to a formulator, collectively that team would meet the requirements of a person of ordinary skill in the art?

MS. CHACON: Objection; legal conclusion.

A. You -- you're asking me to create a legal distinction that I am not trained or qualified to do.

I've set forth what a person of ordinary skill of the art is in paragraph 90, and I have answered the question.

Q. Okay. So that's what I'm struggling with.

You say in your declaration: I was at least a person of ordinary skill in the art by virtue of my clinical background.

I'm not asking you for a legal conclusion. I'm just asking you why -- how that can be true if you do not have a Ph.D. in pharmaceutical sciences or a similar field with at least several years

of experience in the development, manufacture, and characterization of therapeutic proteins, including for example fusion proteins or antibodies?

A. I don't understand your question. I really don't.

It's defined in 90 that a person of ordinary skill in the art would have been a multidisciplinary team.

Q. Okay.

Are you, Donald D'Amico, a multidisciplinary team?

A. A person of ordinary skill of the art would have been a multidisciplinary team.

Q. Okay. I understand -- let me back up.

Was this definition of a POSA in paragraph 90 provided to you, or did you provide an opinion about what the POSA should be?

A. It -- it arose as a consequence of processes between the individuals in the preparation of the declaration. It was part of my education also as

preparation for this -- this -- this effort.

Q. Okay. So, simpler question.

Were you told to assume that this is the definition of a person of ordinary skill in the art for purposes of this case, or did you offer an opinion, does paragraph 90 reflect your opinion about what a person of ordinary skill in the art would be in this case?

A. Paragraph 90 is an -- is a legal definition that I am -- I am not trained or licensed to provide.

Q. Okay.

A. So it's --

Q. And then so factually, though, you say: As a matter of fact - because you're attesting to this in paragraph 91 - I was at least a person of ordinary skill in the art by virtue of my clinical background.

And I understand, I understand your position is that you would have had access to a formulator and that would have -- together you and the formulator

would have formed a multidisciplinary team that collectively would meet the requirements of the POSA.

Am I right so far?

A. Correct.

Q. Okay.

So, when you say "I was at least a person of ordinary skill in the art by virtue of my clinical background," what you mean is "I was a person at least qualified under paragraph 1 to participate in a multidisciplinary team"?

MS. CHACON: Objection; mischaracterizes testimony.

A. Yeah, I -- I don't -- you're taking me into legal terrain that I -- I cannot parse your description. I'm sorry.

Q. Okay.

Do you -- are you as an individual a multidisciplinary team?

A. I don't -- obviously statement -- statement 1 indicates that a person of ordinary skill of the art can be a multi -- multidisciplinary team. So I'm not aware of all the legal possibilities

for an individual to be considered a team.

Q. Okay. I'm not asking about any legal possibilities.

I'm just asking whether you, Donald D'Amico, consider yourself to be a multidisciplinary team.

MS. CHACON: Objection; asked and answered.

A. Again, I can't answer the question.

Q. Okay.

When you meet someone, do you say "Hi, I'm Dr. Donald D'Amico, a retinal specialist," or do you say, "Hi, I'm Dr. Donald D'Amico, a multidisciplinary team"?

A. Obviously the question is absurd, but I'm also a surgeon. I'm a mentor. I'm a counselor. I'm a chair. I'm a clinician. I'm a father. So I wear -- have many roles.

So the distinction that you're drawing, while you've taken it to, you know, an extreme, there are many roles that I play.

So consider oneself a team, do

you consider oneself multidisciplined?

So I think it could -- I think it is something that I can't clearly answer.

Q. Okay. So --

MS. CHACON: Counsel, I'm just -- before you go on, I'm just cognizant of the time with the court reporter and the videographer for lunch purposes. I defer to you when you want to do that, but --

MS. KAYALI: Well, I'll -- I'll defer to Dr. D'Amico.

Up to you. Would you like to take lunch now?

THE WITNESS: What time is it?

MS. CHACON: I think it's 12 --

MS. KAYALI: Just quarter to 1-ish.

THE WITNESS: Let's do it at 1.

MS. KAYALI: Okay. Take a break at 1, got it.

THE WITNESS: Is that okay for our --

MS. KAYALI: Well, the second

most important person in the room, Madam Court Reporter, is that okay with you?

All right.

BY MS. KAYALI:

Q. Okay.

Do you know whether Dr. Falconer relied on your opinions in forming his?

A. I presume he did, but I'm -- presume he did.

Q. How did he come to understand what your opinions were?

A. I've already described the -- to the limit that I can, the collaborative process that would have -- that took place in the preparation of these materials.

Q. Okay. I'm not talking about the preparation of your declaration. I'm asking about how you communicated with Dr. Falconer.

So, I think you said you had a conversation with him, right?

A. Yes.

Q. Okay.

Do you know if he reviewed your

signed declaration?

A. I assume he did, but I'm -- I'm certain he did. In terms of -- whether it was signed or not at the time he reviewed it, I cannot attest, and when he reviewed it I cannot attest. He may have seen a draft copy.

Q. Okay.

But it would certainly make sense to you that before forming opinions of his own that rely on your opinion, he would review your declaration?

MS. CHACON: Objection; calls for speculation.

MS. KAYALI: I'll strike that.

We can move on.

BY MS. KAYALI:

Q. Okay. Can you turn to page 66 of your declaration?

Do you see the legal standards?

A. I'm on bottom page 66.

Q. I apologize. I -- I used the wrong numbers. I'm on page 67, paragraph 110.

A. Got it.

Q. Okay.

Can we look at paragraph 116? That's the definition of "prior art."

Do you see that?

A. Yes.

Q. Okay.

And in paragraph 116 you say: I understand that documents and materials that qualify of prior art -- as prior art - excuse me - can be used to invalidate a patent claim as anticipated or obvious.

Right?

A. Yes.

Q. Okay.

And that's what you were engaged to do in this case, to -- to use prior art to invalidate the patent claim, right?

A. Yes.

Q. Okay.

And then you go on to say in paragraph 118 that: Counsel for Alvotech has informed me that when assessing whether a claim is obvious, I should consider the scope and content of the

prior art, the level of ordinary skill in the art, the differences between the prior art and what is claimed, and any secondary evidence that may indicate the claims are not obvious.

Do you see that?

A. Yes.

Q. And is that the legal standard you applied in forming your opinions?

A. Yes.

Q. Okay.

I want to understand, sort of, there are one, two, three, four parts to that standard, right?

A. Yes.

Q. Okay. I want to just, kind of, get an orientation to where those parts are reflected in your declaration.

And I'm sorry to make you, sort of, flip back and forth between what's now paragraph 118 and the table of contents, but if we start with the scope and content of the prior art, am I correct in understanding that you address that in Section 10, or roman X, "Prior Art to the

'036 Patent"?

A. Okay. Let's find Section 10. I see Section 11.

Q. I think --

A. Yes. Yes.

Q. Okay.

And then subsection 2 "The Level of Ordinary Skill in the Art," that was the definition of the POSA we just looked at that was provided by counsel, right?

A. Yes.

Q. Okay.

Where do you describe the differences between the prior art and what is claimed?

A. Where do I define the differences between the prior art?

Q. I'm looking at that third section of paragraph 118 "The Differences Between the Prior Art and What is Claimed."

Where do you address that?

A. I don't -- is there a -- is there an ob -- I do not see in 118 an obligation to address all four of those.

I see an obligation to consider, but not an obligation to write about all four of those.

Are you assuming that there's an obligation that I write about all of them?

Q. I'm not -- I'm not making any assumptions at all.

I'm just asking where in your declaration I can read and understand your analysis of the -- excuse me, the differences between the prior art and what is claimed.

Where do I know your opinions are about that?

A. I would need -- I would need to review my declaration in detail to provide you.

If you have some reference within my declaration, otherwise I'll need to read through the declaration.

I'm not immediately aware of any section in which I described that.

Q. Okay.

So you're not immediately aware sitting here today of having considered

the differences between the prior art and what is claimed?

A. No, I'm not aware of having described it in my report.

Q. Okay.

A. I didn't say I'm not aware of having considered it.

Q. Okay.

You're just not aware of offering that opinion in your report?

A. Correct.

Q. Okay.

And then you say, Section 4: Any secondary evidence that may indicate the claims are not obvious.

Do you see that?

A. Yes.

Q. What does that mean?

A. If there's something that was -- you know, was -- surfaced later that showed there was a problem with something that I thought was obvious but it was, in a sense, untaught, to use your term, something that would, you know, discover that you couldn't apply a prior art claim

in a manner of -- that was obvious.

Q. Give me a for example.

A. It would be discovered that all patients who received a suntan lotion that everybody was using with the common ingredients but with one minor change, they all developed green hair, that would -- that would render the prior -- that would be something secondary evidence to indicate the claims are not obvious. You would not be able to apply your -- your formulation to.

But I don't know if I've described anything like that, and I'm clearly speculating here.

Q. Okay.

So you didn't consider whether others had tried and failed to make the claimed invention, right?

A. I -- I didn't say I didn't consider. I said I didn't write about them, to my knowledge.

Q. Okay.

You didn't set forth an opinion about those in your declaration?

A. Correct.
Q. Okay.
Same goes for the commercial success of the product at issue?
A. I -- I don't understand. Where are you refer -- could you point to where you're referring to commercial success in my declaration?
Are you referring to -- we're in paragraph 118, are we not?
Q. Okay.
So you don't understand commercial success to belong to any of these categories?
A. I -- I didn't -- I'm not excluding anything by -- I don't understand why suddenly commercial success is an item that I would be excluding from prior art.
Where -- please clarify your question regarding commercial success that came at me from left field, forgive me.
Q. Do you con -- well, that's okay.
Suffice it to say you don't know how the commercial success of an invention

impacts a conclusion of obviousness?
A. I don't.
Q. Okay.
Do you understand how the fact that others tried and failed to make an invention impacts the conclusion of obviousness?
A. It sounds legal to me, and I don't have the qualifications to understand that.
Q. Okay.
Do you understand the concept of teaching away?
A. I have a vague understanding of it. I obviously used the phrase, you know, four minutes ago, but...
Q. Okay.
And that was -- what is your understanding of it?
A. My understanding is that additional information can come to light to invalidate or suggest the invalidation of prior information.
Q. I see.
So if something happens at time

one and then you get more information at time two, you have to consider the information at time two and how that affects the information you had at time one?

A. It could be -- it would be -- again, it would be a piece of data in the vast array of data that one would consider.

Q. When you're forming your opinions, let's say, as of May 2018, do you view things -- do you -- do you give any primacy to more recent data?

A. I consider all the data.

Q. Okay.

Okay. So, can we turn back to "Summary of Opinions," which I think is on -- in paragraph 13? Do you see that?

A. Yes.

Q. Okay.

You say: Ground 1: It is my opinion that a POSA would have been motivated to combine Vitti, the AU Eylea Label and --

A. That's 14, but okay.

Q. I apologize. You're very right.

This is paragraph -- I'm looking at paragraph 14. It says: Ground 1: It is my opinion that a POSA would have been motivated to combine Vitti, the AU Eylea Label, and Larson with a reasonable expectation of success.

Do you see that?

A. Yes.

Q. How would the skilled person have combined Vitti, the AU Eylea Label, and Larson? In what way?

A. So let's start with Vitti. Vitti discloses in its patent that a concentration of aflibercept up to 115 -- 100 plus or minus 15 milligrams per mL, it taught that concentration.

Number two, the Australian label indicated that 8 milligram dosage of Eylea was administered to several patients and was generally well tolerated.

And number 3, Larson describes in detail the viscosity properties of various formulations but indicates that a viscosity between 5 and 15 centipoise

would be -- is taught.

So those three -- those three comprise the basis of my ground for rendering the '036 patent claim obvious for.

Q. So -- okay. So, maybe I'm not fully understanding. Maybe I'm not asking a very good question.

You say the POSA would have been motivated to combine these one, two, three references.

What would the result of that combination have been, in your opinion?

A. An 8 milligram dose of Eylea in a -- in a volume of about 70 microliters with a viscosity between 5 and 15 centipoise.

And there was strong motivation in the community to go to higher doses. We knew that 8 milligrams was safe. We knew that it was disclosed that 115 microgram per -- milligram per mL was taught, and we knew that a viscosity between 5 and 15 centipoise was also taught. Give it to me, I want to inject

it in my patients.

Q. So, it's your testimony that the skilled person --

MS. KAYALI: Well, strike that.

Q. You go on to say -- you say: with a reasonable expectation of success.

What did you mean there?

A. That I would have a reasonable expectation of success, that I -- based on the available information -- information available to me at the time, that such a formulation would be helpful to me for my patients.

Q. Okay.

You don't have any basis to have a reasonable expectation of success that such a formulation would be makable by a formulator, right?

A. Oh, I do. Larson -- I have had conversations with, you know -- Vitti -- excuse me, Larson teaches that such protein concentrations are achievable.

Q. With aflibercept?

A. Yes. Larson teaches that a protein concentration with a -- a wide

range of viscosities is achievable.

Q. What viscosity would the skilled person target?

A. Between 5 and 15 centipoise or less than 20, preferably less than 10. So those are all referenced in prior art.

Q. What's the maximum injectable viscosity for an intravitreal injection?

A. It is out --

MS. CHACON: Objection; vague.

A. It's outside my scope of expertise.

Q. Okay.

You defer to Falconer on -- excuse me. You defer to Dr. Falconer on viscosity issues, right?

A. In general, yes.

Q. Okay.

You say in the second sentence there: It is further my opinion that these references teach, or at least make obvious, the methods recited in Claims 1, 4 through 38 of the '036 patent.

Right?

A. Yes.

Q. Okay.

What do you mean -- what's the difference between "teach" or "making obvious" in that -- as you used it in that sentence?

A. I'm afraid that's a legalism, but I understand that "teaching" is what a -- teaching is what I can find -- found in a specific document.

"Obvious," to me at least as a non-lawyer, strikes me as a broader claim. For example, if the -- if the head of Regeneron got up on the top of the Empire State Building and screamed out, you know, "This is a concentration I'm going to make tomorrow," that would be obvious information. I'm not sure it would be considered teaching.

So, "obvious" to me is things that are available to the person of skill of the art at the time. "Teaching" is a term that I had reserved for what's available in written documentation.

I could be incorrect. It sounds to me to be a legalism.

Q. Okay.

Where would the POSA have started, in your opinion?

A. The POSA would have been highly motivated to seek a higher formulation of aflibercept in order to decrease treatment burden and perhaps see if it was delivered higher efficacy. A POSA would have looked at available documentation prior to 2018 and would have discovered that the Australian label indicated documentation of an 8 milligram dose administered to isolated cases that was well tolerated.

A POSA would have then turned to Vitti and discovered that a concentration of 100 plus or minus 15 milligrams of aflibercept was disclosed and taught.

A POSA would have then tried to discover if such a concentration could exist with a viscosity between 5 and 15 centipoise.

And then one would have worked with -- in collaboration with a skilled formulating chemist, to see if such concentration could be made. If one takes

115 and divides it into an 8 milligram dose, we arrive at just a couple of decimal fractions over 70 microliters. So a POSA would have been highly attracted to a 70 microliter dose, slightly higher than the 50 for most drugs but under the 0.9 for Eylea, and that would have been something that we would have been highly interested in to give to our patients.

Q. You said under the 0.9 for Eylea, what do you --

A. For -- for Macugen, excuse me. 0.9 -- 90 microliters for Macugen.

We have one drug that's given -- was given at the time over 0.5, and that was Macugen.

Q. Okay.

A. But the math points us directly to point -- 70 microliters.

Q. In your opinion?

A. In my opinion. Vitti teaches the math to 70 microliters.

MS. KAYALI: Okay.

It is just shy of 1 o'clock, and this is a good a stopping point as

any.

Let's take a lunch break.

THE WITNESS: Yeah, sure.

MS. KAYALI: Okay.

THE VIDEOGRAPHER: The time right now is 12:57 p.m., and we are off the record.

(Luncheon recess taken.)

- - -

A F T E R N O O N S E S S I O N

- - -

THE VIDEOGRAPHER: The time right now is 1:35 p.m., and we're back on the record.

MS. KAYALI: Okay.

BY MS. KAYALI:

Q. Doctor, let's talk about aflibercept.

How is -- what is aflibercept?

A. Aflibercept is an a fuse -- it's a fusion protein which is a portion of the VEGF receptor, and it's utilized for the treatment of neovascular diseases of the eye, among other things.

Q. So it's correct to say that

aflibercept acts as a decoy receptor of VEGF Trap, right?

A. No. It's a -- it's a decoy receptor of VEGF, not of VEGF Trap. It doesn't -- it is VEGF Trap. It's a decoy receptor of VEGF.

Q. Okay.

Can you turn to 41 of your declaration, please?

Are you with me?

A. Yes.

Q. Okay.

How many different isoforms of VEGF are there?

A. Well, I think the -- the ones I'm familiar with are A, B, C, and I believe there's also a D considered, although the difference between platelet growth factor and D is -- is something that I'm not completely clear about, but certainly A, B, C.

Q. Okay. A, B, C, and then there's something called platelet growth factor.

Is that P1GF?

A. Yes.

Q. Okay.
What is P1GT?
A. It's a related -- a related compound.
Q. Okay.
Does it have generally the same effect of VEGF?
A. No, it does not. It's incorporate -- it is also something that is bound to the same receptors, but is -- I'm not an expert on it, but it's -- that's its -- its -- the context I'm describing it in paragraph 41 is that it's something that the VEGF receptor binds.
Q. And it exists in the eye, right?
A. It exists throughout the human body. I presume it exists in the eye.
Q. Okay.
And what's its normal physiological function?
A. I'm not afraid I don't know.
I presume it has something to do with placental growth. Hence the name.
Q. Okay.
Aflibercept inhibits all VEGF

isoforms and P1GF, right?

A. No. It attracts all -- it binds all -- the difference between binding and inhibit would have to be specified, but in a sense, it binds all VEGF isoforms and PlGF.

Q. Okay.

And the way that aflibercept reduces the amount of VEGF and P1GF in the eye is by binding to VEGF and P1GF, right?

A. Correct.

Q. Okay.

So, by binding to VEGF and P1GF, aflibercept prevents VEGF and P1GF from doing their normal functions, right?

A. I -- I'm distracted. It's PlGF.

Q. I'm sorry.

A. Forgive my correction.

Q. No, no, I'm glad you did that. I just can't tell the difference between an L and a numeral in the -- in the document.

A. Nor could I.

And it could -- let's stand for the record it could be P1GF and we would

both be corrected.

Q. All good.

How about I call it platelet growth factor, would that work for you?

A. Right.

Q. Okay.

A. Placental.

Q. Okay. How about I call it the right thing, placental growth factor.

Okay. So, let me -- let me try that again.

Aflibercept binds all VEGF isoforms and placental growth factor in the eye, right?

A. Yes.

Q. Okay.

And by binding all VEGF isoforms and platelet growth factor, aflibercept inhibits VEGF and platelet growth factor from performing their normal physiological functions, right?

A. Well, from performing their abnormal physiologic functions in a macular degeneration lesion.

We presume -- I mean, you just

called it "normal physiological functions," but this is a disease state that we're treating.

Q. I see.

A. So, I mean, it -- the point is moot, but it inhibits their -- it captures -- it traps VEGF and placental growth factor.

Q. I see.

Maybe can we turn back to paragraph 23 of your report?

And, sorry, I should go to -- I should have directed you to paragraph 25 which is on, I think, two pages later. You say: The role of VEGF in the normal development of the eye vasculature is well establish.

Right?

A. Right.

Q. What is that role?

A. VEGF has many functions in -- in -- in the -- in human tissues. It has functions primarily on blood vessels. It directs the growth of blood vessels. It has roles in sprouting new capillaries.

It has roles in neural stability. It has many, many roles in the body, but the chief ones relate to development of the normal vasculature in the eye.

Q. Okay.

A. And in the body. In things like the -- the reason -- well, okay. It -- it is related to vascular processes in both development and in maintenance in many tissues in the body.

Q. Okay. And so let me see if I've got this right.

In normal eyes, you need to have some functional level of VEGF and platelet -- sorry, placental growth factor, but in eyes with, for instance, AMD, the patient has too much VEGF and placental growth factor?

A. Presumably in the area of the lesion, yes. There's a breakdown of normal processes and those vessels become normal, and as a result or as a cause, they -- there's an overabundance of VEGF, and that results in the leakage and other damage that we see in the various

angiogenic eye diseases.

Q. Okay.

And I'm sorry to have you flipping back and forth, but if I go back to, for instance, paragraph 25, what -- what happens if you don't have enough VEGF or placental growth factor in your eye?

A. What happens if you don't have enough?

Q. Right. If you have too little.

A. I -- I can't -- that would be -- your body always has some VEGF.

I don't know a consequence of going below normal. I'm not aware of that condition.

Q. Okay.

So you're not aware of the clinical effect of going -- of going below normal in terms of the amount of VEGF or placental growth factor in a patient's eye?

A. I am not.

Q. Okay.

Again apologies for the flipping back and forth, but going back to

paragraph 41 where you start talking about aflibercept.

Do you know how many molecules of aflibercept is takes to bind to one VEGF molecule?

A. I -- I'm not sure. I believe it is two. How many molecules, I think one molecule of aflibercept has two binding sites, as I recall. And -- but the binding sites will have a variable residence of the amount of time that they hold the VEGF. There will be some, you know, kinetics about whether they hold it forever or partially release it, et cetera.

But I believe one molecule of aflibercept binds two molecules of VEGF. I mean, that would be my first approximation.

Perhaps I've commented on it in my review. That's a highly technical fact.

Q. It's relevant to dosing, right?

A. Yes.

Q. Okay.

And what is the half-life of aflibercept?

A. I would have to review my document. Let's see if I've commented on it in my document.

If you have the number somewhere, it would help me. Otherwise I don't remember if I commented on it specifically in my document. I'm happy to review my document to see if I can find it.

Q. Okay. I hear what you're saying.

Do you mention the half-life of aflibercept in paragraphs 41 or 42?

A. 41 or 42, no.

Q. Okay.

What is the molecular weight of aflibercept?

A. I -- I would have to review my document again to see is it mentioned. My first recollection is it's on the order of, let me see if I have this right, 114 or so, but I'd have to review my document.

If it's mentioned specifically,

I'm happy to review the document if I comment with precision.

Q. That -- that information of half-life and the molecular weight would be relevant to dosing, right?

MS. CHACON: Objection; calls for speculation.

A. Yeah, would be relevant. Would be relevant, yes.

Q. Okay.

A. Yes.

Q. What was the concentration of the Eylea formulation that was approved for administration as of May 2018?

A. As of -- you're speaking of high dose or low dose?

Q. As of May 2018.

A. I'm trying to remember which was approved. I need to know when the approval date of high dose was.

Q. Okay. Well, how about let's just talk about low dose then for now.

Do you remember what the concentration of low dose was?

A. 40 milligrams per mL.

Q. Okay.

And in forming your opinions as to what the skilled person would have done as of May 2018, you also took into account high dose Eylea?

A. Yes.

Q. Okay.

And high dose Eylea is what is described in the '036 patent, right?

A. Yes, it's 114 and something and change milligrams per mL.

Q. Okay.

And the information disclosed in that patent, the work of those inventors was something you took into account when you were forming your opinions on obviousness, right?

A. Yes.

Q. Okay.

And in your view, what the inventors disclosed in that patents made it more likely that the claims were obvious?

A. Yes.

MS. CHACON: Objection; vague.

BY MS. KAYALI:

Q. Okay. You describe some other anti-VEGF agents.

I forget where they start. The first one I think is pegaptanib, which is I think is Macugen?

A. Yes.

Q. Okay. That's at paragraph, I think, 65.

You were a clinical investigator for Macugen, right?

A. No. I was the -- I was a member of the safety committee --

Q. Oh.

A. -- at Macugen. I did not inject patients with the drug.

Q. Okay.

Are you familiar with the results of the Macugen clinical trials?

A. I am.

Q. Okay.

What is Macugen?

A. Macugen is an aptamer, a PEGylated aptamer that was used to inactivate certain sub-isoforms of VEGF by

intravitreal injection.

Q. Okay.

So an intravitreal anti-VEGF agent?

A. Yes.

Q. Okay.

Where would the POSA in May of 2018 have looked to find out the results of the clinical trials for Macugen?

A. Macugen trials were -- Macugen was the first pharmaceutical approved for intravitreal injection for. So they would have looked to the literature and abundant presentations and widespread experience with the agent.

Q. I see.

How many molecules of pegapt -- pegapta -- Macugen, how many molecules of Macugen does it take to bind to one VEGF molecule?

A. I don't know. I don't know. I presume -- I presume one. But again, it may be that it's going on and off with different molecules, but I would presume it's a one-to-one relationship.

Q. Okay.

And what was the approved dose for Macugen?

A. The dose I would need to refresh my memory from a table. But I remember the approved volume was 90 microliters.

Q. Okay.

And do you see in paragraph 66 that the dose was --

A. 0.3 milligrams.

Q. Okay.

Do you recall from the Macugen clinical trials whether any other doses were tested?

A. I believe there was -- there was a lower dose tested, or maybe a higher dose.

Q. Okay.

Did you review the literature on the doses tested for Macugen in forming your opinions here?

A. Did I -- did I review beyond my knowledge? Yes. I'm aware of the use of Macugen, but did not perform a detailed re-review of Macugen because this drug is

little used at present.

Q. Okay.

But -- so you didn't take a look at whether Macugen clinical trials tested higher or lower doses than 0.3 milligrams, right?

A. I -- I presented results of the clinical trial to the FDA at their DODAC panel, and as a result, with the accumulated experience, I'm extremely familiar with Macugen and did not re-review the specifics of the study because the drug has fallen into disuse.

Q. I see, but I -- I'm just thinking about its dosing now.

So for purposes of forming your opinions in this case, did you consider whether increasing the dose of Macugen resulted in a greater efficacy or longer duration of the drug?

A. Macugen did not figure in my -- in a major way in my considerations regarding this -- the dosing.

Q. Okay.

But you agree that if there are

some anti-VEGF agents for which increasing the dose does not increase the duration of efficacy, that would be important information to consider, right?

MS. CHACON: Objection; calls for speculation.

A. Yeah, there -- there are drugs that are not dose sensitive and there are drugs that are very dose sensitive and there are drugs that have harmful effects at higher dose.

So in general, such information is useful, but nothing specific to anti-VEGF and certainly nothing specific to Macugen.

Q. Okay.

What's the half-life of Macugen?

A. I would need to review my report.

Is it mentioned in my report?

Q. I'm not aware that it is. I don't see it in paragraph 65 or 66.

A. I do not recall the half-life of Macugen.

Q. Okay.

Do you recall the molecular weight of Macugen?

A. I do not recall the molecular weight of Macugen.

Q. Okay.

And the concentration of Macugen, that's -- I -- I could find that number out by dividing 0.3 milligrams into 90 microliters, right?

A. Correct.

Q. Okay.

Okay. Let's go to paragraph 67. That's ranibizumab, right?

A. Yes.

Q. What is ranibizumab?

A. Ranibizumab is a, as it says in my declaration, a recumbent humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. It is an affinity-matured, or affinity-enhanced region of a prior compound which is known as bevacizumab, or Avastin. It is a fragment of it but also been highly modified for use within the eye.

Q. Okay.

Did you consider the half-life of ranibizumab in forming your opinions?

A. No.

Q. Okay.

Did you consider the molecular weight of ranibizumab in forming your opinions?

A. No.

Q. How many molecules of ranibizumab does it take to bind one molecule of VEGF?

A. The -- the construction of the mol -- of the antibody has two binding sites. So I would presume one molecule binds two moieties of VEGF.

Q. Okay.

And then at the end of the paragraph you refer to the Harbor Trial, right?

A. Yes.

Q. Okay. And you say -- well, you cite at the very end of that paragraph for the results of the Harbor Trial Exhibit 1039.

Is that the investigator's

publication?

A. I believe it's Allen Ho's publication with co-investigators of the Harbor Trial, but I will verify by looking at the table of exhibits.

Q. Okay.

A. 1039 -- no, that's Michael Stewart. You're referring Michael -- Michael Stewart here.

Q. What's the difference between that and the --

A. Well, Michael Stewart is a -- is a different publication.

The -- the Harbor Trial was reported out in my table of references as Allen Ho, and we need to find Allen Ho.

Q. I see, okay.

A. Yeah, it's 1026 is the relevant exhibit.

Q. Okay.

So, in paragraph -- I lost it. In paragraph 67 you cited -- you didn't cite the Harbor Trial data. You cited Dr. Stewart, right?

A. Yeah, a later summary of the

Harbor Trial -- Harbor Trial data.

Q. And, sorry, which? You said 1026, right?

A. Yes, Allen Ho, 1026.

Q. Okay.

Is Dr. Stewart's summary a later summary of Dr. Allen Ho's results?

A. I believe so, yes. Let me verify, but I believe so.

It's 102, what? Stewart is 1039. 2012.

Nope, it's the opposite.

Q. Okay.

So Stewart wrote a review paper in 2012, and then two years later, Dr. Ho published the results of Harbor, right?

A. He published the two-year results. One-year results were also available prior to Allen Ho's paper.

Q. Okay.

So Allen Ho's paper just has more results than Dr. Stewart had?

A. Correct.

Q. At the time he wrote his review?

A. Correct.

Q. Okay.

Sorry, I meant to ask you about this earlier, but I had forgotten the document.

MS. KAYALI: I'm going to mark what I think will be 2045.

(D'Amico Exhibit 2045, Macugen Highlights of Prescribing Information, Bates ALVOTECH 1048, was marked for identification, as of this date.)

BY MS. KAYALI:

Q. Okay.

What is this?

MS. CHACON: Counsel, do you have a copy?

MS. KAYALI: I'm so sorry about that.

MS. CHACON: That's okay. Thank you.

A. The die -- document in front of me is entitled "Highlights of Prescribing Information." And then it goes on to be related to Macugen.

Q. Okay.

As a skilled person in May 2018,

what would this document motivate you to do?

A. I would have to read the document.

Q. Let's -- is there a summary section you could read that would answer the question?

A. What is the question?

Q. The question is as of 28 -- May 2018, what would this document have motivated the skilled document to do?

A. The document would have motivated the skilled person to utilize Macugen 0.3 milligram administered once every six weeks by intravenous in -- intravitreous into the eye to be treated.

Q. And how do you know that?

A. Because that's the first thing describing that it's indicated for use in macular degeneration.

Q. Okay.

And you're looking under, like, the dosage and administration section?

A. Yeah. Yeah, you asked me to look at a summary. I presume the most

important information is at the front, but I could be mistaken.

Q. Do you want to take -- let's take maybe a minute or two to -- so you can flip through the document and see if there's anywhere else you think you would look or anything else a POSA would have been motivated to do.

A. (Witness reads document.)

Okay. I have a initial familiarity with the document.

Q. Okay. So let me just ask the same question again, and I'm really just asking if you have the same answer. Let me -- let me find my question.

As a skilled person in May 2018 seeking to develop a higher dose anti-VEGF formulation, what would this document motivate you to do?

A. It would motivate me to utilize macular -- Macugen for the treatment of neovascular wet age-related macular degeneration.

Q. At what dose?

A. 0.3 milligrams.

Q. Because that's the dose that's mentioned in the indications and dosing section?

A. That's the dose that was FDA approved.

Q. Okay.

All right. I think we talked about -- sorry, you can set that aside.

We talked about ranibizumab.

Can you turn to page -- or, excuse me, paragraph 68? I want to talk about bevacizumab.

Okay. What is bevacizumab?

A. It's a -- it's Avastin. It's an antibody that was developed primarily as a cancer therapy, full-length antibody, humanized monoclonal antibody.

Q. And what's the molecular weight of bevacizumab?

A. I would have to reference other material. I don't believe I cite it in my report, or perhaps it's in a table, but I don't know offhand.

Q. Okay.

A. It's big.

Q. It's big?
A. It's big. It's probably 149, 150, something in that range would be my educated guess, but again I would have to cite literature to come up with a precise number.
Q. Okay.
What is the half-life of bevacizumab?
A. I don't know off the top of my head.
If you can point to my report where I cite it.
Q. I -- I don't believe you did. I'm just -- I'm trying to understand that means you didn't consider the half-life of bevacizumab, right?
A. I did not consider the half-life of bevacizumab.
Q. Okay.
Did you consider how many molecules of bevacizumab it takes to bind one molecule of VEGF?
A. I did not consider. I -- I'm aware of its clinical use, but not -- not

its use on a molecular basis.

Q. What's the approved formulation of -- sorry. What is the concentration of the approved formulation of bevacizumab for intravitreal injection?

A. As of 2018, there was no approved formulation of bevacizumab for intravitreal injection.

Q. So how did clinicians decide, with the absence of a label, what dose to use?

A. It's off-label therapy.

Q. It's off-label therapy, I -- okay.

How -- given that there is no approved dose, clinicians have to pick a dose when they're injecting, right?

A. Right.

Q. How -- how do clinicians do that?

A. Phil Rosenfeld at Bascom Palmer initially studied a group of patients with I believe it's 1.25 milligrams. I'd have to, again, look at my document. And that dose was, kind of, plucked out of the air

by him and became more or less the standard. I -- we can check, I think it's 1.25 milligrams. It's 50 microliters.

It doesn't say in my report, but it's -- there -- in South America they use 2 1/2 milligrams, I believe, and -- but it's a completely freeform between you and the patient, no FDA approval, compounded pharmacy stuff that you buy a vial of the cancer therapy and you tell your compounding pharmacist, Hey, I want you to aliquot a bunch of these 'cause I'm going to give them to eye patients.

So it's -- it's not quite the Wild West, but it's typical off-label therapy.

Q. Okay.

Do you know if anyone has ever compared whether increasing --

MS. KAYALI: Excuse me. Strike that.

Q. Do you know whether anyone has ever compared different doses of bevacizumab to see whether higher doses have a longer or better effect?

A. In what disease?

Q. Any of the diseases that anti-VEGF agents treat.

A. I'm not aware, and I don't believe I've commented on studies. There are studies that compare bevacizumab with other things, but not a dose-ramping study of bevacizumab. Perhaps they exist, but my preference is -- is not to use bevacizumab because of its off-label characteristics, so I'm less inclined to be interested in it.

Q. I see. But in forming your opinions for purposes of this case, I believe you opined that increasing the dose of an anti-VEGF agent would increase its duration of action, right?

A. Oh, yes.

Q. Okay.

So if there was evidence about what -- whether increasing the dose of bevacizumab did or did not increase the efficacy or duration of action, that would have been pertinent information, right?

A. Possibly.

Again, I'm not interested in bevacizumab because it's not an eye formulation. It's used off-label. There have been episodes of endophthalmitis from improper pharmacy construction.

So I consider it in a different category than the FDA-approved agents.

Q. I see.

So you're distinguishing between aflibercept versus Macugen, Lucentis --

MS. KAYALI: Excuse me, strike that.

Q. You're distinguishing bevacizumab on the one hand from Macugen, Lucentis, aflibercept, right?

A. I'm distinguishing -- let's get the grouping right.

Macugen I don't use. I was very involved in the study. I don't use it. It's little used today.

Bevacizumab is a, as I mentioned, a Wild West compound that we formulate, and there have been episodes -- epidemics of endophthalmitis. Publications have appeared where the

compounding pharmacy dosing and syringe preparation of bevacizumab have given doses all over the map. So the data for bevacizumab is much less reliable than the data we have for certainly than ranibizumab, aflibercept, and even Macugen.

So if you can ask me your question. That -- I did not consider studies that related to bevacizumab dosing in formulating my opinions regarding this -- this issue.

Q. Okay.

So if a -- if a study reports on the dose of an anti-VEGF agent that's not approved, that wouldn't be pertinent to your opinions in this case?

MS. CHACON: Object --

A. It would be --

MS. CHACON: One moment, Doctor.

Objection; mischaracterizes testimony.

Go ahead.

A. It would be less reliable than agents with a -- less reliable than

FDA-approved agents for the reasons I cited. That is one compounding pharmacy may make a certain concentration. Another compounding pharmacy make another. Another compounding pharmacy may make one that's loaded with bacteria. That's different from a drug that's gone through GMP processes and has, you know, a standardized vial and all of that testing.

And so the reliable dosing information will be much more formidable for an FDA-approved agent that's applied in GMP-approved packaging than from something that we get from a -- from a compounding pharmacy, you know, to be determined.

Q. I see, okay.

In your opinion, though, you can infer from what happened --

MS. KAYALI: Let me strike that.

Q. In your opinion, information about the duration of a dose and the effect of increasing --

MS. KAYALI: Strike that.

Q. In your opinion, information

about whether increasing dose increases duration of effect in one intravitreal anti-VEGF agent provides an expectation about whether the same thing will be true in a different anti-VEGF agent, right?

MS. CHACON: Objection; mischaracterizes testimony and opinions.

A. I'm not -- without specific information. Again, the -- the study would determine -- the study would determine that the motivation might be to try, but the -- drawing inferences is not the way one ensures safety in a patient's eye.

Q. Okay. Maybe I'm asking a simpler question.

For purposes of forming your opinions in this case, did you consider whether increasing the dose of one VEGF agent and seeing that it increased the duration of effect of that agent informs what you would expect to happen with a different anti-VEGF agent?

MS. CHACON: Objection; asked

and answered.

A. I think I've answered the question.

Q. I'm sorry, I don't think you have. Let me see if I can ask it more clearly.

The duration of effect of a dose of one drug, let's say Lucentis, in your opinion, informs what the skilled person would have expected regarding the duration of effect of aflibercept, right?

MS. CHACON: Objection; calls for speculation; mischaracterizes testimony.

A. So, I'm -- I'm trying to understand your question.

So, you're asking me if -- if more is better, if more is always better.

Is that your question?

Q. Maybe.

So, I guess I'm trying to -- I'm more focused on, like, what you can extrapolate from one drug to another, okay. So we've got this class of drugs, they're anti-VEGF agents administered

intravitreally.

A. Right.

Q. Are you with me? And we've talked about, I think, four of them: Aflibercept, Lucentis, Macugen, and bevacizumab. Right?

Okay. In your opinion, if a trial for one showed that increasing the dose increased the duration of effect, would you expect that increasing the dose would increase the duration of effect in one of the other four drugs?

MS. CHACON: Objection; asked and answered; calls for speculation.

A. Yeah. So, but your question is devoid of context.

So, at the very beginning when Macugen was approved, there were no other anti-VEGF drugs being injected into the eye, none, zero. So everyone was terrified of what -- could there be systemic effects, could there be this, could there be that. So there was a tremendous motivation to utilize the lowest possible dose that was effective at

that point in time. That was the motivation for selection of the 0.3 milligram dose of Macugen, or 3 milligram, whatever it is.

Then as therapy became widespread and we realized there was this tremendous injection burden. The Macugen label permitted no exceptions. Every month you needed to show up in the clinic, bring grandfather to the clinic every single month. The community began searching for ways to prolong the duration or improve the effect -- efficacy while minimizing the treatment burden. So that led to the Harbor Trial which was done, and that trial was looking at ranibizumab to see whether or not ranibizumab increasing the dose by a factor of four would improve duration.

So, the context is, I think, important of how doses were selected. At the beginning, it was terror over what could anti-VEGFs do off-target. Later on when the recognition that we were going to have tens of thousands, if not more,

injections every year to deal with in patient visits, the community sought improved therapies for both efficacy and duration.

Q. Okay. I'm not -- I'm not trying to talk about any one drug in particular.

I'm just asking if you have in the prior art -- if the POSA can see in the prior art that for some anti-VEGF agents, increasing the dose leads to a longer duration of action, would the POSA believe that understanding provides a reasonable expectation of success for increasing the dose and thereby achieving a longer duration of action in a different anti-VEGF drug?

MS. CHACON: Objection; asked and answered.

A. I think I've --

MS. CHACON: One second, Doctor.

Calls for a legal conclusion.

A. I think I've answered the question.

Q. I -- I have to disagree because I'm still just not sure what the answer

is.

If the POSA -- it's your opinion in this case that if you increase -- that as of May 2018 the skilled person would have expected that if you increase the dose of aflibercept you would have -- that it would have had a longer duration of action on patients. Right? That's the premise of your opinion is?

A. Yes.

Q. Okay.

So, my question is if the prior art showed that there was a clinically meaningful difference in the efficacy, durability, or safety of a higher dose of ranibizumab being as compared with, you know, the low dose form, that would support your conclusion, right?

MS. CHACON: Objection; asked and answered.

A. It would support but not eliminate the need for trial with the specific drug. It would be -- it may -- it -- and that would also depend on various trends within the data.

If it was completely negative, that would be one thing. However, if it showed an indication that it was positive, that would be another thing.

Q. Okay.

And conversely, if the higher dose of ranibizumab did not show any clinically meaningful difference in efficacy, durability, or safety compared with the 0.5 milligram dose, that would undermine your opinions, right?

A. No, because that did not occur.

You introduced the phrase "clinically meaningful." There was a difference in the ranibizumab study. The PRN group had fewer injections, so the only conclusion that one can draw from the ranibizumab study is that it was a resounding success, that a higher dose had greater efficacy than the lower dose. It was not a clinically meaningful difference. It did not result in product. It wasn't worth the cost of going through GMP and FDA approval, but the only indication in the data is that the higher

dose was better. And all things being equal, if, after the day the Harbor Trial was published, given that the efficacy was the same and the safety was same and the duration was a bit longer, I would have switched and used 2 milligrams, and I bet everybody else would too.

But viewed at through the lens of clinically meaningful, which means are you going to make a new drug and get a company to spend $800 million on it, no, it was not clinically meaningful, but it was different in the right direction supporting higher dosage.

Q. Okay.

And in your opinion, the POSA would be motivated to do things that are not clinically meaningful then?

A. A POSA would be motivated to do things that are not clinically meaningful. How would I know -- how would a POSA know something is not clinically meaningful before one attempts it with a specific drug?

I don't understand how that

question could relate to my frame of mind at that moment.

I would be encouraged by the results of Harbor that a higher dose of an anti-VEGF and not an aptamer, in this case an -- a protein compound, showed improved durability in the eye. I would have taken that as a strong indication to look at other protein drugs such as aflibercept for longer duration and et cetera.

Q. Irrespective of whether the authors of the study concluded that the dose did not show any clinically meaningful difference in efficacy, durability, or safety?

A. Yeah, "clinically meaningful" is the key phrase there. We can -- we can argue all day long, but they also state that the PRN group had fewer injections, and that's what a POSA would have looked at. Hey, it's -- it's certainly not worse than 0.5. If anything, it's better. Maybe we didn't study enough patients. Maybe 4 milligrams would be -- would have shown a difference. But the door remains

wide open after Harbor and, in fact, to me is encouraging, to a POSA would be encouraging.

Q. And the same would have been true if studies comparing bevacizumab, your -- you would equally rely on studies showing doses of bevacizumab or Macugen, right?

A. No. I would discount studies of bevacizumab because, as I've said, the doses are prepared by random off-label pharmacies with high variability which is well-documented in epidemics of poor sterility. Comparing them and Macugen is not a protein compound. It's the only aptamer -- to my knowledge, no aptamer until recently has ever been approved for human use. So it's a completely different agent.

Comparing FDA protein-related compounds would be relevant, but not -- not bevacizumab. I do not cre -- give the highest level of confidence to the bevacizumab dosing data for the reasons that I've outlined.

Q. Okay.

The best evidence, though, of whether increasing the dose of aflibercept would increase its duration of action would come from comparing a higher dose of aflibercept to a lower dose of aflibercept, right?

MS. CHACON: Objection; vague.

A. Would the best -- let me -- let me try to run your question again so I understand it.

The best evidence -- the best -- re -- can you repeat her question to me?

Q. Sure. And maybe "best" is a bad word.

As compared with data showing the effect of increasing dose on the duration of ranibizumab effect, if you're -- a study comparing the effect of increasing dose of aflibercept on the duration of aflibercept effect would provide more direct evidence about what was likely to happen if you increase the dose of aflibercept, right?

A. Well, yeah, I agree with that.

Q. Okay.

And do you know whether anyone ever compared the duration of effect of a higher dose of aflibercept with a lower dose of aflibercept?

A. I do.

Q. Okay.

And what -- where was that done?

A. That was done in the CLEAR-IT trial.

Q. Okay.

Which CLEAR-IT trial?

A. CLEAR-IT 1 and 2. CLEAR-IT 1 is, I think, the more germane.

May we reference it in my report?

Q. So, what makes it more germane?

A. Well, it's the initial study. They looked at 4 milligram dose in, I believe, 28, 27 patients.

Q. Okay.

A. But I would have to refresh myself with looking at my report and see.

Q. Okay.

So, if you turn to paragraph 44,

I think you'll find your reference to the CLEAR-IT study.

Do you see that?

A. Yep.

Q. Okay. Why don't you take a moment to read paragraph 44?

A. (Witness reads document.)

Okay.

Q. Okay.

And you said CLEAR-IT 1 was informative because it compared a higher dose to a lower dose, right?

A. Yeah.

And CLEAR-IT 2 is also -- as I refresh myself, CLEAR-IT 2 is also certainly germane to this issue that we're discussing.

Q. I see. And that's because there are actually multiple injections of a higher dose compared to a lower dose of aflibercept, right?

A. Well, it's just 159 patients compared to I believe it's 28 -- 21 patients.

Q. Okay.

And in CLEAR-IT 1, patients received a single injection, right?

A. Correct.

Q. Okay.

And in CLEAR-IT 2, patients received multiple injections, right?

A. Yes.

Q. Okay.

What -- in CLEAR-IT 1 you don't describe in paragraph 44 any conclusions about whether the 4 milligram study or the -- excuse me, the 4 milligram dose lasted longer than the 0.5 milligram dose, right?

A. Not described in paragraph 4.

Q. You describe --

A. 44.

Q. Do you describe that elsewhere?

A. Not to my knowledge. Or perhaps I have to look through the document.

Do you have it elsewhere?

Q. Well, I'm genuinely asking. I don't know the answer.

A. Nor do I.

Q. Okay.

A. But I'm happy to read my document in full, if that will --
Q. Well, you agree at least that --
A. In this paragraph there's no conclusion about the CLEAR-IT.
Q. Okay.
And then you say -- or, sorry. You're citing Exhibit 1034 there, right?
A. Yes, that's Quan Nguyen.
Q. Okay.
And if you flip to paragraph 12, that's your materials considered list, that is -- I'm sorry, you probably just said this and I just didn't pick up on it. 1034 is Quan Nguyen and that's the author's manuscript of the -- of the CLEAR-IT 1 study, right?
A. That is correct.
Q. Okay.
Then we get -- you start talking about CLEAR-IT 2 in paragraph 45, right?
A. Correct.
Q. Okay.
And in paragraph 45 you say: Developers hope to show that aflibercept

could be dosed less often than monthly.

Right?

A. Correct.

Q. Okay.

And it randomized 159 patients to receive three injections of 0.5 or 2 milligrams or single doses of 0.5, 2 or 4 milligrams with final evaluations at 12 weeks, right?

A. Correct.

Q. Okay.

And then you go on on the next page to say: In the next phase, patients were followed from week 12 to -- excuse me, 16 through 52 and given injections as needed.

Right?

A. Yes.

Q. Okay.

And an average of two injections was required with a meantime to first injection of 129 days, right?

A. Yes.

Q. And you say: Patients treated as needed required fewer injections yet

maintained excellent gains in vision.

Right?

A. Yes.

Q. Okay. And you say: Patients receiving three monthly loading doses achieved superior visual results compared with those achieving single injections.

Right?

A. Yes.

Q. Okay.

Where do you describe the duration of effect of a 4 milligram aflibercept dose in comparison with a 2 or 0.5 milligram dose?

A. I don't -- I don't see it specifically described in either of these two paragraphs, and I'm unaware if it's described elsewhere in my declaration.

Q. Okay.

Well, presumably you would expect the 4 milligram dose to -- well, if increasing the dose increases duration of action, you'd expect the 4 milligram dose to have longer efficacy, less time -- or, sorry, longer time to reinjection and

fewer overall injections, right?

A. Well, let's remember the CLEAR-IT 1 -- no. The answer is no.

The CLEAR-IT 1 study looked at an eight-week endpoint. So, at eight weeks, those differences might not be apparent.

Q. Well --

A. Long --

Q. Sorry. Please go ahead. I didn't mean to cut you off.

A. Yeah. Eight weeks may not be enough time to, you know, to look at the efficacy. So the efficacy of CLEAR-IT 1 I believe was at eight weeks. So, you know, I can --

Q. I'm sorry, I'm talking about CLEAR-IT 2. And maybe it would be easier to do it with the document in front of us.

You cite Exhibit 1039, right?

A. Yes.

Q. Okay.

And that's that Stewart review paper we've been talking about?

A. Do we have it as an exhibit?

Q. I'm about to hand it to you, yes.

So, this has been marked as Exhibit 1039.

Okay. Are you familiar with this document, Doctor?

A. I am.

Q. Okay.

When's the last time you looked at it?

A. Probably within the last four days.

Q. Okay.

A. Within the last four days.

Q. Okay.

Take a moment, but my question is going to be about some text on page 6 where I think Stewart discusses the Phase II CLEAR-IT 2 trial.

A. (Witness reads document.)

Q. And I'm happy to wait, Doctor. I just want to make sure you're not waiting for a question from me.

A. No, I'm not.

Q. Okay.

A. Thank you.

(Witness reads document.)

Okay. I'm ready.

Q. Okay.

Dr. Stewart discusses the Phase II CLEAR-IT 2 trial on page 1180 of his paper, right?

A. Yes.

Q. Okay.

And he describes the Phase II CLEAR-IT trial as randomizing 159 patients to receive three injections of 0.5 milligrams, 2 milligrams, or single doses of 0.5 milligram, 2 milligram or 4 milligram with final evaluations at twelve weeks, right?

A. Yes.

Q. Okay.

And then he goes on to say: Although the reduction experienced by the patients receiving injections every four weeks exceeded that of patients treated only once --

MS. KAYALI: Excuse me. Strike that. I'm -- I misspoke.

Q. He says: Visual improvement at week eight was similar in patients receiving single doses or three doses.

Right?

A. Right.

Q. Okay.

And where does he explain -- where does he compare the results of the 4 milligram dose to the 2 milligram dose?

A. I don't see that he does in this paragraph.

Q. Okay.

That would be relevant information, though, in determining whether or not a higher dose of aflibercept has a longer duration of action, right?

A. No.

Q. Why not?

A. If I put a 25 pound block of ice on the table, a 10 pound block of ice on the table and a ice cube on the table and come in two hours later, the second -- the first two would still be on the table.

I don't know at eight or twelve

weeks if that difference would necessarily be apparent. The limitation is the time of the study. We're talking about duration of effect, and yet we have only one time point in the study beyond twelve weeks. So ex -- investigators were looking at things less often than every eight weeks. Even every 16 weeks was being considered at that time.

So the fact that they're equivalent right out of the gate doesn't mean that if they had followed the patients for longer they wouldn't have had an effect.

Q. They would have had to follow them for, like --

A. 16 weeks.

Q. 52 weeks?

A. Well, 52 weeks there's -- there's additional treatment going on. But again, with one time point, he -- the conclusion here is at 12 weeks, the average macular thickness, and where he says where it's comparable, yeah, there -- there's no comparison given, but we know

the baseline is at twelve weeks. Again, both drugs could perform very well at twelve weeks, but one could fall off the cliff at 16 weeks. We cannot tell that from the available information.

Q. In -- in Stewart, right?

A. In Stewart.

Q. Okay.

If that information were available, that information would be relevant to determining whether increasing the dose of aflibercept would increase its duration of action, right?

A. I believe so.

Q. Okay.

Goes on -- Stewart goes on to say: During the second phase of the CLEAR-IT 2 study, patients were followed from week 16 through 52 and given injections as needed.

Right?

A. Yes.

Q. Okay.

So this part of the study is going to tell us more about the duration

of effect of increasing the dose of aflibercept, right?

A. The original study would, yes. He comments only on the 2 milligram every four week dose here.

Q. I'm sorry, what do you mean "the original study would"?

A. Well, I mean, he -- he's commenting on a -- on a -- on a study that was already reported, correct?

So he says here the -- he's commenting on a subgroup, patient initially treated with 2 milligrams every four weeks in that -- in that paragraph.

Q. Sorry, I got to break that down because I understand part of it but not the other part.

So, I think what you're saying is Stewart doesn't comment on any observed differences between 2 milligrams and 4 milligram doses, right?

A. Correct.

Q. Okay.

The original study publication would have that information?

A. Presumably.
Q. Okay.
And that information would be important to consider in figuring out whether increasing the dose of aflibercept would increase its duration of action, right?
MS. CHACON: Objection; vague.
A. Yeah, it would be -- it would be informative given the restrictions of the time point studied and the fact that, you know, we have only 12-week data, et cetera. You know, is there -- there's other data, but now we've administered additional injections.
We also have some patients in loading dose. So it would be a complicated analysis.
Q. Okay.
But this is -- that would be more direct evidence than, for instance, imputing an effect for ranibizumab data, right?
MS. CHACON: Objection; vague.
A. If the trial of the

ranibizumab -- the trial of the ranibizumab data, I presume you're referring to Harbor, was conducted very, very similar to a registration trial, much as the VIEW 1 and VIEW 2 trials were conducted.

The CLEAR-IT trial was an investigator-initiated presumably corporate-sponsored trial, and so there's different parameters, different things that are studied, different ways of looking at it.

So when you say it would be more directly comparable, you know, comparing one registration trial versus another given the -- all the problems of different drugs might be at times more informative than comparing an investigator-sponsored trial with a registration trial of the same drug. I think that's an arguable point. I know it is.

Q. Okay.

Is that your opinion? If you want to know whether you would increase the dose of aflibercept -- or, excuse me.

Is it your opinion that if you wanted to know whether increasing the dose of aflibercept would increase its duration of action, you'd be better served by looking at whether increasing the dose of ranibizumab would increase its duration of action than by looking at aflibercept data?

A. No.

Q. Okay.

Where did I go wrong?

A. Nowhere. I just said -- you asked better. I think that, yes, the odds are that it would be better, but it -- not -- not completely. There might be circumstances that would render data from a randomized trial be more helpful.

This is -- the -- the CLEAR-IT 1 study was, you know, one was 21 patients. The CLEAR-IT 2 is 159 patients. I don't recall how many patients are in Harbor, but it's hundreds of patients, hundreds and hundreds of patients in each of the subgroups. So that would -- in the totality of evidence, that would figure in

my evidence.

If you're asking me to say which is the single best, I wouldn't be thinking in terms of single best. I would be thinking of what is the totality of evidence that a person of ordinary skill in the art would have to draw a reasonable chance of success that a higher dose of a drug would be successful, and they would all be elements of my decision.

Q. Okay.

So what you're saying is you would have started with the premise that you wanted to dose 8 milligrams of aflibercept and then looked in the art to see if there was any disclosures that 8 milligrams would work, right? And you take -- consider that in the totality of the evidence?

MS. CHACON: Objection; mischaracterizes testimony.

A. No, I would have started with the teaching that 8 milligrams of aflibercept was administered and generally well tolerated by patients, and I would

have looked to other currents at the time, motivation at the time, other data at the time that suggested that higher doses were possible, and then I would have looked for evidence as to what kind of concentration could be made and what kind of formulation could be made with an appropriate viscosity, but I would have started with the teaching that 8 milligrams of aflibercept was generally well tolerated.

Q. Okay. And we'll come back to the 8 milligram point.

I just want to clarify something you just said. You would have looked for evidence as to what kind of concentration could be made and what kind of formulation could be made with an appropriate viscosity.

Those aren't things you have any opinions about though, right?

A. What do you mean I don't have any opinion?

Q. Well, you defer to Dr. Falconer for issues of concentration and viscosity, et cetera, right?

A. It would be a mutual discussion. There are issues of volume of injectate, et cetera. So it's not -- it's not like I tell him something and walk away. It's a -- it's a mutual process, a conversation between us.

Q. Okay.

And did you have that conversation in this case?

A. By conversation I mean communication.

Q. Okay.

Did you have those communications in this case?

A. Yes.

Q. How so?

A. That's privileged information, I believe.

Q. No. Unfortunately if you've relied on someone else's opinion or if they've relied on yours, that's not privileged information.

So I'm asking how did you have those conversations --

A. By mean --

Q. -- with Dr. Falconer?
A. Sure. By means of the collaborative process that I've described as a person of ordinary skill in the art as a member of the team.
Q. Okay.
And how did you communicate with your other members of the team?
A. Through -- through the counsel.
Q. So counsel told you what Dr. Falconer's opinions were?
A. No. There were also -- there were also written communications and other elements of the teamwork.
Q. Okay.
When did Dr. Falconer write to you?
A. I don't recall.
Q. Did he write to you?
A. I don't recall.
Q. Okay.
So were there written communications?
A. I don't recall.
Q. So why did you say that there

were also written communications?
A. Because there were many, many documents going back and forth, and I don't recall who authored one or the other, et cetera.
Q. So it's your testimony that there were also written communications but you don't recall whether there were written communications with Dr. Falconer?
A. Correct.
Q. Help me make sense of that.
A. Well, there -- there are communications from -- from my counsel describing themes that were work --
MS. CHACON: And again, Dr. D'Amico, I'm going to caution you and instruct you not to answer the substance of any attorney communications with you.
You can answer her question to the extent it involves communications between you and Dr. Falconer directly, but otherwise I'm going to instruct you not to answer.
THE WITNESS: Yes.

BY MS. KAYALI:

Q. Okay.

So, my question is about your communications with Dr. Falconer, okay. And I think this is -- is really important because I need to know what you relied on in forming your opinions, and I need to know what he relied on in forming his opinions.

A. Sure.

Q. I need to know what written communications there were between you and Dr. Falconer.

A. Yeah, I don't believe -- I don't recall written communications between me directly and Dr. Falconer.

Q. Okay.

So when you say "written communications," you're describing that the lawyers told you what Dr. Falconer's opinions were?

THE WITNESS: Am I permitted to answer that?

MS. CHACON: You can answer that yes or no.

A. Yes.
Q. Okay.
So you took the lawyers at their word for what Dr. Falconer's opinions were, right?
A. Until the conversation, yes.
Q. Okay.
When was that conversation?
A. It's -- we've already gone over that. I believe I've answered that.
It's listed in my document, I believe, as June and in his document as -- apparently it's September. Is that correct?
Q. And you don't remember which one it was?
A. No.
Q. Okay.
And you don't remember whether you read his declaration before you --
MS. KAYALI: Well, strike that.
Q. You recall reviewing his declaration so that you could verify his opinions, but you don't recall whether that declaration was signed when you

reviewed it?

A. Yes.

Q. And you don't recall when you reviewed it for the first time?

A. Yes.

Q. Okay.

Do you recall how long the conversation was?

A. Lengthy, but I -- you'd have to give me some standard.

Q. I don't know what "lengthy" means.

Do you think it was more than two hours?

A. Probably about that.

Q. Okay. He testified that it was about 30 minutes long.

A. I don't recall. As I said, I don't recall.

Q. Okay.

So don't remember whether it was two hours, 30 minutes, five hours?

MS. CHACON: Objection; asked and answered.

BY MS. KAYALI:

Q. Do you remember where you were when you had that conversation?

A. I don't recall.

Q. Okay.

You don't remember whether you were in the U.S. or outside the U.S.?

A. I'd need access to my calendar to tell you.

Q. Okay.

What did he tell you on -- in the conversation?

A. We discussed the various themes that had been developed over the course of our teamwork.

Q. What themes?

A. The possibility of creating formulations with a concentration of 115 milligrams per mL with a viscosity between 2 and 15 centipoise.

Q. Okay.

And what led you to ask him whether it would be possible to create such formulations?

A. Oh, because those were the

specific targets that were taught by Vitti, the Australian label, and Larson.

Q. What did you tell Dr. Falconer? Did you -- did you tell Dr. Falconer that the skilled person would use an 8 milligram dose?

A. I don't recall in that conversation if I told Dr. Falconer that -- those specifics, but I certainly was, by that time of the conversation, long familiar with Vitti, the Australian label, the Larson patent and the other patents that we've been discussing, or not discussing.

Q. You were familiar with them -- am I right in understanding that your opinion in this case was really here's what this skilled clinician would want, they'd want a dose of 8 milligrams and they'd want it -- well, and what else? What else was your opinion? They'd want to, what, inject it in a volume of 50 milliliters?

A. Yeah, that high volumes are bad. If you can avoid them, that's good. High

viscosities are bad. If you can avoid them, you'll make an injectate that's easier. It's got to be able to stay on a shelf. We don't want to deal with, you know, refrigerators if not necessary. It should be able to be made sterilely, et cetera, et cetera. All the elements of our -- of a -- of a skilled drug formulator.

But we are already using agents in our clinic, so a point of comparison was very strong.

Q. Sorry, what does that mean "we are already using agents in our clinic"?

A. Well, he -- he would know that it's not something that we're going to store in a deep freeze three floors away.

If we're giving, you know, 50 of these out a day, we want to be able to have something that's conveniently stored in our clinic and can go through a 30-gauge needle, et cetera, in an appropriate volume that's safe for the pressure of the eye.

Q. Okay.

And so your job was to figure out what dose of aflibercept the skilled person would want to administer, in what volume, and then it was his job to figure out whether the skilled formulator could make such a formulation?

A. Yes. And with the appropriate viscosity, the third element, that would allow me to inject it through a 30-gauge needle.

If he makes tar that has that concentration, it's no good to me. If he makes an acetone-like liquid that drips out of the syringe all over the floor, that's no good to me. So there's an optimal viscosity range. That's why Larson teaches 5 to 15 centipoise viscosity. You don't want it too high or too low.

Q. Okay.

And it was your opinion, as you informed Dr. Falconer that in no uncertain terms, 8 milligram was the right dose that the POSA would want to use?

A. Eight -- as I -- as I've already

clarified, 8 milligrams was the signal event revealed in the Australia patent that, you know, that I would say precipitated the chain of -- of thought to create an 8 milligram dose.

Q. Okay.

And it's your opinion that the POSA would have been motivated to create precisely an 8 milligram dose, not something higher than 8 milligrams?

A. Correct, because it was also taught in Vitti that 115 milligrams per mL was the upper limit of -- of the teaching, and so dividing 8 milligrams into -- at 115 milligram per mL, one comes out at 70.09 -- whatever it is. Of course our syringes are only graded in .7, .8, .9. So for a clinician staring at a syringe drawing up a compound, one would certainly select 70 as the initial target volume.

Q. Okay. So help me understand.

I thought you didn't have any opinions about what concentrations were achievable. I thought you relied on Dr. Falconer for that?

A. No, I rely on Dr. Falconer for formulation. The volume, the volume is what I am coming up with. The dose and the volume of the injection.

Vitti taught 110 milligram per mL. I'm looking for an 8 milligram dose. Do the math and it comes out to 0.70 microliters, just a little bit different of that. And the syringe gradations are such that 70 microliters is the formulation a clinician is going to use because syringes are not marked in finer gradations than that. So that's what I relied on him for formulation, but not for my volume target.

Q. What do you mean a syringe is not marked in finer gradation than that?

A. Well, I -- the syringe is marked at, you know, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and one-tenth of an mL.

If I were to target a dose of -- of 8 milligrams, I would come up with a -- on a syringe, it would be .7019, I would have to redo the math, but it would come out from practical terms you'd be looking

at a 70 microliter injection.

Q. Okay.

So it's your testimony that the POSA would not have considered injection intervals of point -- 0.15, 0.25, 0.35, 0.45, or 0.55, right?

A. I did not say would not have considered. They certainly could consider .0001, but dismiss them out of hand for impossibility of viscosity requirement. So the phrase "do not consider" I don't agree with.

We would consider a range something -- the target range would -- ideal would be 70. 60 or 50, they would also be acceptable, but 70 is the initial calculation that I would ask as a person of ordinary skill in the art.

If somebody told you that you could make commercially available FDA drugs available at, you know, .00001, we would do it tomorrow, less volume in the eye, less people waiting in your clinic with high pressure. That's not possible as a formulation. But to say that they

wouldn't be considered I think is inaccurate.

Q. Okay. So there's a lot to unpack there.

So, you think it -- all other things being equal, as you said earlier, you'd prefer to give less volume in the eye, right?

A. Yes.

Q. Okay.

And most drugs at this time were dosed at 50 microliters of volume, right?

A. Except for Macugen which was at 90 microliters of volume.

Q. Okay.

So you would be aiming for as close to 50 as you can get, right?

A. No. I'd be aiming for -- in general, yes. I would want as low a volume as I could get with an injectable formulation, yes.

Q. Okay.

And then it, sort of -- - and you want 8 milligrams in your formulation, right?

A. For sure.
Q. And then you're -- you kind of say, Over to you, Dr. Falconer, tell me what I can get. Right?
A. At -- well, I -- my -- Dr. Falconer, I initially calculate that this 8 milligrams I have information, I've been taught that 8 milligrams could be made in approximately 70 microliter volume, is that possible.
Q. Okay.
And you say that because, in your opinion, the highest dose -- excuse me, the highest concentration of a protein formulation that Vitti discloses is 115 mgs per mL?
MS. CHACON: Objection; vague.
A. I -- I say it because I've been taught that 115 milligrams per mL of aflibercept is a taught -- is a taught concentration in Vitti.
Q. Okay.
And I think what I heard you say is that's the highest concentration Vitti teaches, right?

MS. CHACON: Objection; mischaracterizes testimony.

A. I -- I'd need to see the patent, but I believe that's correct.

Q. Okay. Because otherwise if you could have higher concentrations than that, you could go to lower volumes, right concentration?

A. If you could have higher concentrations you could go to lower volumes?

Q. If you wanted 8 milligrams and you could have concentrations higher than 115 mgs per mL, you would be able to inject them in a lower volume?

A. Well, I believe Vitti also discloses other ranges of concentrations, or other ranges of concentrations have been disclosed, but I keyed on Vitti as a teaching.

As I understand it, the fact that there are other ranges does not preclude one from using a teaching of a specific concentration rendering it obvious. I could be wrong, but I would

need advice of counsel to answer that question more precisely.

Q. Okay.

So you would need advice of counsel to understand whether if Vitti discloses multiple ranges of concentration for protein formulation, choosing one of these ranges is sufficient to render a claimed formulation obvious?

A. I think it --

MS. CHACON: Objection; mischaracterizes testimony.

Go ahead.

A. I believe that Vitti dis -- Vitti teaches in the first -- in the first sentence of its patent in that relevant paragraph, which I'm happy to look at, that it can be used at a con -- it could be formulated at a concentration up to 100 plus or minus 15. I think that's the most important -- I took that as the most important portion of that paragraph, and I believe a person of ordinary skill of the art would utilize that -- that number.

Q. Okay. We can come back to that.

But in any event, your -- your opinion is predicated on the idea that Vitti teaches a target concentration of 115 mgs per mL. Is that right?

MS. CHACON: Objection; mischaracterizes testimony.

A. Rephrase -- restate -- my -- is predicated on?

Q. Your opinion is predicated on the idea that Vitti teaches the target concentration of 115 mgs per millimeter of protein formulations, right?

A. Yes.

Q. Okay.

And that of the various ranges of protein concentration formulation Vitti discloses, your opinion is predicated on the fact that the skilled person would select 115 mgs per mL, right?

MS. CHACON: Objection; vague.

A. Yes.

Q. Okay. Let's go ahead and take a look at Vitti. This has been marked Alvotech Exhibit 1007.

Okay. And if you turn to --

I'll give you a moment to familiarize yourself with the document.

A. I'm okay.

Q. You're okay, okay.

Then I'll give myself a moment to pull it up.

(Pause.)

Q. Okay. So, if you turn to your opinion in Ground 1 of your obviousness analysis, and that begins on -- I think in paragraph 160.

Do you see that?

A. Okay. Let me go there.

I have it.

Q. Okay.

What is your opinion regarding -- what do you disclose as your opinion regarding Vitti?

A. In -- want me to read this? Is that what you're asking?

Q. Well, I'm asking your opinion about what Vitti discloses.

A. Vitti discloses that a concentration of 100 plus or minus 15 milligrams of mL of a VEGF antagonist, a

range, up to that range, from 5 -- plus or minus 0.075 to 100 plus or minus 15 milligram per mL of a VEGF antagonist.

Q. Okay.

And where is that disclosure in Vitti?

A. I'm reading in item 94 in the patent.

MS. KAYALI: All right.

Sorry, could we go off the record for a second? My computer is malfunctioning, and I just need a moment.

MS. CHACON: Sure.

THE VIDEOGRAPHER: The time right now is 2:59 p.m., and we are off the record.

(Recess taken.)

THE VIDEOGRAPHER: The time right now is 3:18 p.m., and we're back on the record.

BY MS. KAYALI:

Q. Okay. Dr. D'Amico, at any time during one of our breaks, lunch, did you discuss the substance of your testimony

with counsel?

A. No.

Q. Did you discuss any of the legal standards applying to the case?

A. No.

Q. Okay.

Could you please turn to paragraph 197?

A. Of Vitti? We were on Vitti.

Q. I'm sorry, no, of your -- of your declaration.

A. Okay.

Q. Okay.

You say: A POSA would have taken Vitti's disclosures and employed basic and routine mathematics to calculate the dosage in milligrams of aflibercept in each embodiment based on the POSA's understanding described above that the injection volume should be limited to 100 microliters.

Right?

A. Yes.

Q. Okay. And, I'm sorry, you say -- when -- when you say "each

embodiment" in paragraph 197, you're referring back to paragraph 196, right?

A. Yes.

Q. So when you're referring to about 80 milligrams per milliliter, about 90 milligrams per milliliter, or about 100 milligrams per milliliter --

A. Where -- where are you seeing 80?

Oh, I see. Yes.

Q. Okay.

And you're citing paragraph 94 of Vitti for that -- that statement, right?

A. Yes.

Q. Okay.

You then use the about 80 mgs per mL, about 90 mgs per mL, and about 100 mgs per mL disclosed in Vitti and say that the POSA would have understood that to equate to a dose of about 8 milligrams, about 9 milligrams, and about 10 milligrams in paragraph 197, right?

A. That's correct.

Q. Okay.

They would equate to -- the 80 mgs per mL embodiment, the 90 mgs per mL embodiment, and the 100 mgs per mL embodiment, those would equate -- in a different volume would equate to different doses, right?

A. Yes.

Q. Okay.

And you have testified, I believe, that the POSA would be aiming for 50 microliters, but it would accept anything up to a hundred microliters, right?

A. That would be a desirable range, but lower would be better.

Q. Lower would be better, okay.

So, an 80 mg per mL aflibercept solution in a volume of 50 microliters, how many are -- what dose is that?

A. I'd have to calculate it.

Q. I have a calculator.

A. If you have it.

Q. I don't have the number. I do have a calculator.

Do you -- do you have your phone

handy?

A. No.

Q. That's an honest answer. If you'll give me one moment, we don't even have to go off the record. It's in the other room. I'll be right back.

THE VIDEOGRAPHER: I'm sorry, counsel. Go off the record?

MS. KAYALI: No, we can stay on. I'll be back in 30 seconds.

(Pause.)

BY MS. KAYALI:

Q. Okay. Sorry about that. Here's a calculator.

A. And the math you want me to perform? If you could repeat.

Q. Sure.

So if you -- you explain that Vitti's disclosure of about 80 mgs per mL, about 90 mgs per mL, and about 100 mgs per mL would be a disclosure to the POSA of 8 milligrams, 9 milligrams, and 10 milligrams of aflibercept, right?

A. Yes.

Q. And you rely on that in support

of your position that the skilled person would have been motivated to use 8 milligrams of aflibercept because Vitti discloses it, right?

A. No.

Q. No? That's not what you say?

A. Well, it's -- I also mention that I'm targeting 8 milligrams because of the Australian patent.

Q. Okay.

But you're also relying on Vitti, right?

A. Yes.

Q. Okay.

A. Yes.

Q. So Vitti is one of the reasons why --

A. Right.

Q. -- you think the POSA would have been motivated to use 8 milligrams?

A. Correct.

Q. Okay.

And you describe that first in paragraph 196, 197, and you then turn to the Australian label in 198, right?

A. Yes.
Q. Okay.
So now my question is why did you -- let me ask a better question. You said a range of volumes would have been acceptable.
What would an 80 milligram per milliliter -- what dose of aflibercept would an 80 milligram per milliliter formulation disclose if the POSA thought a volume of 50 microliters was appropriate?
A. So, 8 -- so, we're talking about one-twentieth of that, so that would be a 4 milligram dose.
Q. Okay.
And what about the 9 milligram per mL embodiment in 50 microliters?
A. A 9 -- that would be a calculation. So 0.05 times 9 equals, that would be a 0.45 microliter.
Does that sound correct?
Q. I don't know.
A. I don't know either.
Math under pressure is not a -- not --

Q. That's why I became a lawyer.
A. -- is a -- is a team sport, so.
Q. Okay.
A. If it's a -- if it's a higher concentration than the 80, it's going to wind up being a smaller volume. So 0.45 sounds about right to me.
But again, I reserve the right to correct that math if it's wrong.
Q. So, I'm not asking about -- you to tell me the volume. I'm asking you to tell me what the dose would be.
So, I'm asking -- because it's your opinion, or in your testimony in your declaration, that the 80 mgs per mL, 90 mgs per mL, and 100 mgs per mL -- well, let's -- let's back it up.
80 mgs per mL, 90 mgs per mL, and 100 mgs per mL, those are concentrations, not doses, right?
A. Correct.
I think the answer you're looking for is I think it calculates out to 4, 4 1/2, and 5 milligrams for those concentrations, that I see a head shake

down from your team.

THE WITNESS: Is that correct?

MS. SONG: Sorry, I actually not -- sorry.

A. Yeah, I believe that's the calculation.

Q. Okay.

So I think what you're saying is that if the POSA used a 50 microliter volume instead of a 100 microliter volume, the POSA would have understood Vitti to disclose somewhere between 4 and 5 milligrams of aflibercept doses, right?

A. I don't follow you at all.

Q. Okay.

The reason you decided 80 milligrams per -- 80 mgs per mL, 90 mgs per mL, and 100 mgs per mL were disclosures of a dose of aflibercept rather than a concentration of aflibercept is because you multiplied them by 100 microliters, right?

MS. CHACON: Objection; vague.

A. I -- I -- I'm totally lost.

Q. Okay.

A. I would need to see this on paper and --

Q. Well, let's try again at paragraph 196.

A. Okay.

Q. 80 mgs per mL, is that a concentration or a dose?

A. 80 mgs per mL is a concentration.

Q. Okay.

And to figure out what dose you think the POSA would understand from that, you multiply it by a hundred microliters, right?

A. That -- multiplying 80 mgs per mL per mL multiplying by a hundred microliters, no. You would -- you would divide by a -- you would have that dose into a hundred microliters.

Q. I'm sorry, this is why I became a lawyer and not a mathematician. I'm being imprecise with the science -- you know, mathematical operations here. But let's try this again.

You would understand that a

dose, a concentration of 85 mgs per mL in 100 microliters and you do the same thing for Vitti's about 90 mgs per mL embodiment, right?

A. Yes.

Q. And you do the same thing for Vitti's about a hundred mgs per mL embodiment, right?

A. Yes.

Q. Okay.

And my question is because the skilled person -- the skilled person would be aiming for 50 microliters, I'm trying to understand what dose of aflibercept the skilled person would take away from Vitti from these embodiments in a dose of 50 microliters.

So, am I correct that what I would do is divide 80 milligrams per mL by 50 microliters to find that out?

MS. CHACON: Objection; vague.

A. I -- you're -- you're asking me about formulation and math on the fly. I'm afraid I would need to do that on paper, so, and prepare. I don't -- I

don't think it's reasonable under these conditions to start doing calculations.

Q. Okay.

Suffice it to say, though -- well, do you know how to do these calculations?

A. I do.

Q. Okay. You just don't want to do them right now?

A. I don't feel -- I don't feel it's appropriate. You're confusing questions about concentrations, various numbers, et cetera.

We can try it. If you'll give me some time to do it, I'm very, very happy if you'll pre-specify and I'll take time to check my answers, et cetera. I do not want to commit to calculations that I have not had relaxed and composed time to -- to do. I'm a very careful person.

Q. Okay. So, if --

A. If you perform them, I'm happy to check them and verify them.

Q. Okay. So, to get 80 --

MS. KAYALI: Well, let's strike

that.

Q. You're not willing to do the calculations right here, right?

A. I'm uncomfortable doing them for fear of being inaccurate in a serious proceeding.

Q. Okay.

You didn't do them in forming your opinions in this report, right?

A. No.

Q. Okay.

And the POSA could do them, right?

A. Yes.

Q. Okay.

And you agree that if you used, for instance, a 50 microliter injection volume instead of a hundred microliter injection volume, you would -- the POSA would arrive at doses lower than 8 milligrams, right?

A. If -- if you used a -- with what -- starting with what concentration?

If the POSA used a 50 microliter compared to a hundred of what?

Q. Volume for injection.

So let -- maybe -- maybe we're making this more complicated than it is.

In paragraph 197 I see that you've done calculations to convert concentrations into dose on the basis of a volume of 100 microliters, right?

A. Yes.

Q. Why did you not also provide calculations using 50 microliters?

A. I don't recall.

Q. Okay.

That would be relevant though, right? That would reflect doses that Vitti disclosed, right?

A. It would be -- it would be interesting, but I had already targeted a -- a concentration of 115 milligrams per mL. So that -- that was the primary concentration I was working on.

There were other concentrations that were possible to permit ranges for the formulation chemist if he was unable to build 115 microliters per mL as an 8 milligram dose with a viscosity of

between 5 and 15, but the -- so it's additional information for him, but it is not anything that dissuaded me from looking at 115 milligram per mL with a target of 8 milligrams at the stated viscosity.

Q. Okay. I'm just confused though 'cause you don't -- I don't think you say anything about 115 mgs per mL being the target concentration here. You're taking Vitti's concentrations, right? 80 mgs per mL, 90 mgs per mL, and a hundred mgs per mL, right, in paragraph 196?

A. Yeah, Vitti -- Vitti teaches 115 milligrams per mL, yes.

Q. Okay. But in order to understand what dose Vitti teaches, you say in paragraph 196: Vitti discloses specific embodiments of about 80 mgs per mL, about 90 mgs per mL, and 100 mgs per mL.

Right?

A. Yes, but I also say in paragraph 96 that Vitti -- again, the dose derives from the Australian patent, not from

Vitti.

Q. Okay.

You say, though, in paragraph 197 that a POSA would have understood each of these disclosures in Vitti fall within the scope of at least about 8 milligrams, right?

A. Right.

Q. Okay.

And you reach that conclusion based on the assumption that the POSA would have administered a formulation containing a concentration of about 80 milligrams per mL, about 90 milligrams per mL, or about 100 milligrams per mL in a volume of 100 microliters, right?

A. Yeah, I consider that subsidiary information.

The -- the -- 196 specifies the teaching of a hundred plus a 15 milligrams per mL. I received as the additional piece of evidence, which I've said many times, the initial impetus was for 8 milligram dose. Vitti teaches up to 115 milligram per mL. The calculation comes

out to 70 microliters.

If my formulation chemist would also like to make different concentrations up to 80, 90, and 100, that information is also disclosed here. 60 and 50, maybe they're possible, but they probably are going to be too viscus to go down a 31-gauge -- a 30-gauge needle, but I do not see 197 being in conflict with 196 or in some way disproving or limiting 196.

Q. Okay. I'm not asking you about what's in conflict. I'm not asking you to defend your opinions. I'm just asking what you did.

You say: A POSA would have understood that each of these disclosures in Vitti fall within the scope of at least about 8 milligrams.

Right?

A. Yes.

Q. That is only the case if you assume that the POSA uses an injection volume of about 100 microliters, right?

A. I didn't follow the --

MS. CHACON: Objection; vague.

Go ahead.

A. I don't follow the question.

Q. Okay.

You have not -- the only basis for your conclusion that a POSA would have understood that each of these disclosures in Vitti fall within the scope of at least about 8 milligrams is based on your calculation in paragraph 197 using a hundred microliters, right?

A. No. My calculation is based on the Australian patent of 8 milligrams and taught by the concentration provided in Vitti in 196. Those are the basis of the obviousness of the claim.

Q. Okay.

So you don't rely on Vitti at all for a disclosure of at least about 8 milligrams of aflibercept, right?

A. I didn't --

MS. CHACON: Objection; mischaracterizes testimony.

A. Yeah, that completely mischaracterizes what I said.

I just said the primary target

was established by the Australian patent taught by Vitti at a certain calculation with a calculation to 0.70 microliters in a viscosity between 5 to 15 centipoise as taught by Larson.

Q. Okay.

How does Vitti -- so, let's -- let's back up. There are a couple of different components of these claims.

I understand you looked for them in the prior art, and I'm now talking about the 8 milligram portion, okay?

A. Mm-hm.

Q. Your opinion that the POSA would have wanted to use an 8 milligram dose of aflibercept, that's based on the Australian label, not on Vitti, right?

MS. CHACON: Objection; mischaracterizes the testimony.

A. Well, I think it's -- I think doses are a thread throughout all the patent, but the primary impetus, yes, is the Australian label.

Q. Okay.

And that's because the

Australian label contains information about isolated cases of overdoses being generally well tolerated?

A. It's clinical data. It's patient data in a -- in a clinical trial. It's people got the drug. So it's high, high confidence information about its performance in the eye.

Q. Okay.

And if you had clinical data suggesting a high, high confidence that doses up to 20 milligrams were well tolerated, you would instead want to go to 20 milligrams, not 8, right?

MS. CHACON: Objection; calls for speculation.

A. Yeah, you're completely speculating.

What do you mean, if I had -- if I had what data for?

Q. Well, you said the reason you would start with 8 milligrams is because the Australian label says that isolated instances of 8 milligram doses were well tolerated, right?

A. Mm-hm.
Q. Okay.
If something else said isolated instances of 20 milligrams were well tolerated, you would have wanted to start with 20 milligrams, right?
MS. CHACON: Same objection.
A. Yeah, there -- there are cases of massive overdose to that level. There's a case reported.
That doesn't necessarily -- the typical jump in a dose escalation trial is four times the current dose, as we saw in Harbor. So 2 milligrams, you know, 0.5 to 2, the 2 milligram aflibercept dose to 4 would be the next logical step for a clinician looking to do dose escalation. I would consider 2 to 20 to be too big a jump. I would not be concerned to do that as the initial step.
And the fact that somebody did it once would not swayed me in that. But in the context of a clinical trial that's listed in an official governmental label, I would be more inclined to follow that

data.

As I've said, data's of different qualities to me.

Q. Okay.

What in Vitti -- sorry. I think we've -- we have heard from you -- okay. Your opinion -- I asked your opinion that the POSA would have wanted to use an 8 milligram of aflibercept is based on the Australian label, not on Vitti, right?

A. Not completely on Vitti, yes.

Q. Not completely on Vitti, okay.

A. Yeah.

Q. So is it partially based on Vitti?

A. The initial impetus is based on the Australian label.

Q. Okay.

Does anything in Vitti teach the POSA 8 milligrams?

A. The calculation of 115 milligrams per mL would support the creation of an 8 milligram dose, yes.

Q. Okay.

So it's your testimony that the

concentration of a hundred -- well, let me -- how? How is that the case?

A. Well, as I've explained I think several times now, I took the 8 milligram generally well tolerated dose that was published in the Australian patent -- in the Australian label, excuse me, and then I looked to prior art that looked for formulations of aflibercept, and Vitti teaches that 115 milligrams per mL is possible, and so I took that and did a calculation and came up with a volume of 70 microliters.

I then looked to Larson to determine what would be an appropriate viscosity range that would be not too thick and not too thin, the goldilocks viscosity between 5 and 15, and worked in collaboration with a formulation chemist to create it. That is the process.

Did I consider other things? Did I consider my knowledge of injection volumes or of dose frequency or all of those things? Of course. I bring my entire body of experience, but the pathway

to arrive at obviousness is just as I have outlined it.

Q. Okay. My question's very different and much simpler.

What in Vitti teaches an 8 milligram dose?

A. I -- I would have to review the patent in detail.

Q. Okay.

So, it is not your testimony that you've provided the answer to that question in paragraph 197, right?

MS. CHACON: Objection; mischaracterizes the testimony and document.

A. So, your -- your -- as I take it, your point is that my pulling a concentration out of the range that is taught in Vitti is somehow not a teaching that 8 milligrams is a possible dose. Is that correct?

Q. No, that's -- I'm not trying to suggest anything. I am asking you.

I understand paragraph 97 which concludes with the sentence: A POSA would

have understood that each of these disclosures in Vitti fall within the scope of at least about 8 milligrams.

Do you understand that?

A. Yes.

Q. That's what I'm looking at?

A. Mm-hm.

Q. Okay.

A. And I think that's true.

Q. You think that's true.

What in Vitti discloses a dose of about 8 milligrams?

A. Vitti gives a range of concentrations from 5 plus 0.075 milligrams to 100 plus or minus 15 milligrams So that's a broad range. And I have pulled out three examples, or two examples of that range.

So Vitti teaches that there's broad range of concentration permissible, and I have selected 8 milligrams because I'm interested in an 8 milligram dose. Vitti certainly brackets 8 milligrams within this range of 5 to 100 plus or minus 15. So clearly Vitti teaches that

an 8 milligram dose is taught. It is -- it is clearly within the range specified, according to my reading as a person of ordinary skill of the art.

Q. Okay.

The embodiments that you plucked out of Vitti's broad range are about 80 milligrams per milliliter, about 90 milligrams per milliliter, and about 100 milligrams per milliliter in paragraph -- at the end of paragraph 196, right?

A. Yes.

MS. CHACON: Objection; vague.

BY MS. KAYALI:

Q. Okay.

And none of those concentrations are 115 mgs per mL, right?

A. That's obvious, yes.

Q. Okay.

If you used a concentration of 115 mgs per mL and you did the same math that you did in paragraph 197 and multiply it by a hundred -- excuse me, divide it into a hundred microliters, you would --

you wouldn't get a dose of 8 milligrams, right?

MS. CHACON: Objection; vague.

A. That's vague.

You would get -- if you take 115 milligrams per mL and you are trying to achieve a dose -- remember, Vitti is the second step in obviousness. I'm already looking for an 8 milligram dose which is fully disclosed by the Australian label.

Vitti shows a wide range. And looking at the highest range to start with to give the clinical formulation chemist the greatest leeway, I would select 115, which the calculations show would be injectable in a 70 microliter volume.

Whether he can build it with a viscosity as desired is -- is unknown, but that's his domain. But all of the elements are disclosed.

Q. Okay. Just trying to understand which elements you're finding in which references.

And my question is you rely on the AU label, the Australian label, to get

you to 8 milligrams and then you move to Vitti for concentration?

A. Yes.

Q. Okay.

You're not relying on Vitti for 8 milligrams of dose, right?

MS. CHACON: Objection; mischaracterizes the testimony; asked and answered.

A. Yeah, I've already answered that.

Vitti is supportive of 8 milligram dose. It's supportive of a -- of a -- of different doses. Vitti is -- Vitti is a broad range.

The target dose -- the target dose is established by the Australian label.

Q. Okay.

So, Vitti discloses a very broad range of doses that you can calculate using the kind of math that you did in paragraph 197, and within that somewhere is 8 milligrams, right?

A. Yes.

Q. Okay.

All right. And now -- sorry, you said something else that confused me, and I just want to figure it out.

Okay. You say Vitti shows a wide range of concentrations, I think you were talking about, a wide range of concentrations, and looking at the highest range to start with to give the clinical formulation chemist the greatest leeway, I would select 115 mgs per mL, right?

A. Yes.

Q. Okay. I want to look at that in your declaration. I think, for example, we can go to paragraph 206.

Okay. And you say: A POSA would have sought to have a high concentration on the upper end of what is disclosed in Vitti.

And in your opinion, the upper end of Vitti's disclosure of -- of concentrations is 115 mgs per mL, right?

A. Yes.

Q. Okay.

If Vitti had disclosed higher

concentrations, you would have started there. If Vitti had only -- if Vitti had stopped at a hundred, you would have stopped there, right?

MS. CHACON: Objection; vague.

A. Not necessarily. I would have been guided by the Australian patent to find a concentration of -- a dose of 8 milligrams at a concentration at a -- in a volume of 115 milligrams per mL, in a concentration of 115 milligrams per mL.

Q. Sorry, I'm just -- I'm focused on that 115. I'm just trying to understand where that comes from, and I think you're testifying that that's -- you get to 115 because that is the high end -- the highest concentration Vitti discloses as acceptable.

MS. CHACON: Objection; vague; mischaracterizes testimony.

A. I don't -- I don't see the word "acceptable" in Vitti. You -- you've added a word there.

Vitti teaches a concentration. The liquid formulations may contain 5.0

plus or minus 7.5 to 100 plus or minus 15 milligrams of a VEGF antagonist.

Q. Okay.

And that's still a VEGF antagonist, right?

A. Right.

Q. Okay.

Sorry, you said you're in paragraph 87?

A. 94.

Q. 94.

So, you're reading: In certain embodiments, the pharmaceutical formulations are liquid formulations that may contain 5 plus or minus 0.75 mgs per mL to 100 plus or minus 15 mgs per mL of a VEGF antagonist.

Right?

A. Yes.

Q. Okay.

And then Vitti provides specific examples within that range of concentrations, right?

A. Some examples. Not the full range, but some examples.

Q. Okay. The ones he provides are 5 mgs per mL, 10 mgs per mL, 15 mgs per mL, 20 mgs per mL, 25 mgs per mL, 30 mgs per mL, about 35 -- sorry, I should have been saying "about" each time. But 35 mgs per mL, 40 mgs per mL, 50 mgs per mL, 60 mgs per mL, 70 mgs per mL, 80 mgs per mL, 90 mgs per mL, or 100 mgs per mL --

A. Or about 100 mgs per mL.

Q. About 100 of a VEGF antagonist such as aflibercept?

A. Right.

Q. Okay.

What does "about" mean in the context of this patent?

MS. CHACON: Objection; calls for legal conclusion.

A. Yeah, I'm not certain, but at the very beginning the first sentence putting 100 plus or minus 15, then about 100 to me as a person of ordinary skill in the art I take that to be anywhere between 85 and 115 because the range has already been specified within the same numbered item.

Q. Okay.

So, in your opinion, the disclosure of about 100 mgs per mL of a VEGF antagonist such as aflibercept is a disclosure of -- sorry, 85 to 115 mgs per mL of aflibercept, right?

A. No, that's not correct.

You're -- I believe you're asking me to draw a distinction of about a hundred and a hundred plus or minus 15. That hinges on a complete legal definition of the word "about," which I am incapable of providing.

However, I relied on the explicit teaching of 100 plus or minus 15 which is stated in the first sentence of that item.

Q. Okay.

So you're -- you're not relying on the about 100 mgs per mL of a VEGF antagonist such as aflibercept?

A. I think I've said numerous times that I'm relying on 100 plus or minus 115 milligrams per mL.

Q. So, I'm just trying to get to

the bottom of 100 plus or minus 15 mgs per mL -- sorry, excuse me. 5 plus or minus 0.75 to 100 plus or minus 15 mgs per mL of a VEGF antagonist, that's what you're relying on?

A. Yes.

Q. Okay.

And VEGF antagonist, that's a -- that's a group of drugs, right?

A. Not in this context. It's specifically -- this item 94 specifically describes "such as aflibercept." So this paragraph is clearly -- the fact that it's all grouped within one paragraph is clearly referring to aflibercept as a person of ordinary skill of the art would read this paragraph.

Q. Okay. It -- I -- I see that the paragraph says "or about 100 mgs per mL of a VEGF antagonist such as aflibercept," but the language of paragraph 94 is -- earlier is: 5 plus or minus 0.75 mgs per mL to 100 plus or minus 15 mgs per mL of a VEGF antagonist.

Right?

A. The language is that, but I think the -- the language is that, but it's clear that this is an -- this is an item that is referring, as the examples are being calculated, to aflibercept.

I think a person of ordinary skill of the art would conclude that 94 relates to aflibercept.

Q. Sorry, I -- I just lost what you said there.

Okay. So the word "aflibercept" -- sorry. So, paragraph 94 says "in certain embodiments," right, and then it goes on to provide the range that you rely on and it says that's a range of a VEGF antagonist, right?

A. Right.

Q. And then it gives an example of things that fall within that range, right?

A. Right.

Q. Okay.

And one of the examples is 5 mgs per mL of a VEGF antagonist such as aflibercept. Another is 10 mgs per mL of a VEGF antagonist such as aflibercept.

And then one example is about 100 mgs per mL of a VEGF antagonist such as aflibercept, right?

A. Right.

Q. Okay.

So the word "aflibercept," the example of aflibercept comes after the language "for example" in paragraph 94, right?

A. It comes after, but within the same item, yes.

Q. Within the same paragraph --

A. Correct.

Q. -- that's your point?

A. No.

And also it's very clear in the way the patent is structured that if you look at item 92, item 92 describes initially the combination therapy in -- in Vitti.

Item 93 describes the anti-angiopoietin aspects of therapy.

Item 94 describes the anti -- the aflibercept part of the therapy, and then item 95 describes co-formulation,

et cetera.

So it's very clear in the structure that a person of skill of the art that this patent is laid out to describe combination, here's the angiopoietin portion, here's the anti-VEGF portion, and now there's co-formulation.

So I -- I stick by my assertion that the entirety of item 94 in the Vitti patent relates to aflibercept.

Q. Okay.

I hear you that some of the paragraphs relate to an ANG2 formulation, right?

A. Right.

Q. And then some the paragraphs relate to a VEGF antagonist formulation, right?

A. Right.

Q. Okay.

And then some examples of VEGF antagonists formulations are given and there -- those examples are given in the concept of aflibercept, right?

MS. CHACON: Object to form.

A. I object to you -- you're again trying to draw the distinction that the one -- the 5 to 15 -- the 100 plus or minus 15 does not -- is not referring to aflibercept.

I think a person of ordinary skill in the art, as I will say again, will read paragraph 94 as we're describing aflibercept concentrations.

Q. Okay. But just time-out for one second.

You understand you can't object to my questions, right?

A. Oh, sorry. Sure.

Q. Okay.

I'm asking a question, and maybe we're talking past each other. You're -- in 94, the words are -- well, let me ask a different question.

Is aflibercept the only VEGF antagonist described in this patent?

A. No.

Q. Okay.

Is the word "VEGF antagonist" defined in the patent?

A. I'd have to read it to -- I'd have to review the patent to describe if it describes "VEGF antagonist" somewhere.

Q. Okay.

And, but you didn't consider what the definition of "VEGF antagonist" in Vitti in the course of forming your opinion, right?

MS. CHACON: Objection; mischaracterizes his testimony.

A. Yeah, that's completely erroneous.

I considered many things in the formulation of my opinion.

Q. Did you consider the definition of "VEGF antagonist" in Vitti as one of those things?

A. Yes.

Q. I -- I don't see it in your report. So tell me how you considered it.

A. I'm aware of what VEGF antagonists are as being a person of ordinary skill in the art.

Q. Okay.

And VEGF antagonist, as a person

of ordinary skill in the art, those include more than just aflibercept, right?

A. Yes.

Q. Okay.

And so the sentence "In certain embodiments, the pharmaceutical formulations are liquid formulations that may contain 5 plus or minus 0.75 mg per mL to a hundred plus or minus 15 mg per mL of a VEGF antagonist" is referring to VEGF antagonists which include but are not limited to aflibercept, right?

A. Not in the context of this paragraph. This paragraph is quite specific describing aflibercept, as my reading as a person of ordinary skill in the art.

Q. Okay.

So it's your testimony that the words "a VEGF antagonist such as aflibercept" mean that "a VEGF antagonist" early in the paragraph can only apply to aflibercept?

A. That is correct.

Q. Okay.

So the patent's definition of "VEGF antagonist" doesn't apply in paragraph 94, right?

MS. CHACON: Objection; calls for a legal conclusion.

A. I didn't say that.

I said in this particular paragraph, the -- it's clear they're describing -- after the ANG2 paragraph, they are describing the aflibercept properties and concentration and then ultimately go on to co-formulation.

I don't think the -- the jux -- the placement of this paragraph and the wording in the paragraph and its -- its conclusion with certain embodiments are -- you know, co-formulation, et cetera, would lead a person of ordinary skill in the art to conclude that paragraph 94 is dealing with aflibercept in its entirety.

Q. Okay.

And so, because of what you just said, when you read the language in paragraph 94 "5 plus or minus 0.75 mgs per mL to 100 plus or minus 15 mgs per mL of a

VEGF antagonist," you're substituting the language of "VEGF antagonist" for "aflibercept"?

A. Yes.

Q. In your reading.

A. In my reading it -- in my reading it's very clear describing aflibercept.

Q. Irrespective of how the patent may otherwise define a VEGF antagonist.

A. Well, it may -- it may -- the -- the next phrase has "of a VEGF antagonist such as aflibercept." I think a person of ordinary skill of the art would assume that the -- would -- would read the entire paragraph as relating to aflibercept.

Q. Okay.

So is your opinion that paragraph 94 in -- is related to aflibercept and only aflibercept or is related to VEGF antagonists including aflibercept?

A. Wow. Let me -- I'm almost tempted to take a break on that one.

Is it my opinion -- can you

please re-read the question?

Q. Of course.

So, I'm treating to understand as a person of ordinary skill when you read paragraph 94, is it your opinion that the words of "a VEGF antagonist" include only aflibercept or include an umbrella of drugs that include aflibercept?

MS. CHACON: Objection; vague.

A. Yeah, I -- I can't -- I can't draw distinction between those two.

Q. So you can't draw a distinction between the class of drugs or whatever the patent defines as "VEGF antagonists" and the term "aflibercept"? That's not something you're able to do?

A. No, I'm not able to do because in the context of a person of ordinary skill in the art it's clear that 94 is relating to aflibercept, in my opinion.

If it also relates to other things, I cannot make a speculative comment, but it's clearly -- the paragraph is clearly formatted to be an aflibercept paragraph following an ANG2 paragraph.

Q. Okay. It's clearly -- sorry, you are distinguishing --

MS. KAYALI: Strike that.

Q. Okay. Let's turn now to paragraph -- can you turn to paragraph 205 of your report? I think that might be where we already are.

Are you there?

A. Mm-hm.

Q. Okay.

So, you say in paragraph 205: A POSA would have understood that Vitti taught that the stable liquid pharmaceutical formulation taught in Vitti may comprise 10 plus or minus 1.5 milligrams to 100 plus or minus 15 mgs per mL of VEGF antagonist and specifically discloses an embodiment comprising about 100 mgs per mL of a VEGF antagonist such as aflibercept.

Do you see that?

A. Yes.

Q. Okay.

So, are you revising that statement in your report on the basis of

the conversation we just had?

A. What are you say -- why would I revise it? I don't see the -- the contradiction on the basis of what I just said.

It says: Specifically discloses. What is "specifically discloses"?

It also discloses 100 plus or minus 15.

So, I -- please point out the contradiction between what is read and what -- I -- forgive me, I do not understand your question. Maybe that's the best way to say it.

Q. Okay.

So, my question is you say: Vitti taught a stable liquid pharmaceutical formulation may comprise 10 plus or minus 1.5 mgs per mL to 100 plus or minus 15 mgs per mL of VEGF antagonist and specifically discloses an embodiment comprising about 100 mgs per mL of a VEGF antagonist such as aflibercept.

Right?

A. Yes.
Q. Okay.
You do not say here that Vitti specifically discloses an embodiment of 5.
A. Yes, I see that. It must be elsewhere in the patent, or else it is an error.
Q. Okay.
So, do you know if it's an error?
A. I would have to re-read the entire patent and see if a range of 5 is -- a range of -- of 10 is listed, but certainly 5 -- actually, the statement of 10 to 100 plus or minus 15 is certainly true because 5 is lower than 10.
Q. Okay. But you're quoting from Vitti, right, to --
A. Right. It could be an error. As I've admitted, it could be an error.
Q. All right. So there might be some errors about what Vitti discloses in your declaration here, but when you're talking about the specific embodiment of aflibercept, you point to the "about 100

mgs per mL of a VEGF antagonist such as aflibercept" language, right?

A. Yes, that is one example.

Q. Okay.

And it's the only example you mention in paragraph 205, right?

A. Yes.

Q. Okay.

And you also point to paragraph 87 for disclosures of acceptable --

A. Paragraph in my disclosure or paragraph in a patent?

Q. In paragraph 205 of your declaration, you also point to paragraph 87 as disclosing formulations of VEGF antagonist, right?

A. Let me find -- you're talking about my paragraph 87.

Q. No, I'm talking about your paragraph 205 which cites paragraph 87 of Vitti.

A. Of Vitti, okay.

Q. As disclosing a reason that the skilled person would have selected 115 mgs per mL of aflibercept formulation, right?

A. Yes.
Q. Okay. Paragraph 87 discloses a range of 5 plus or minus 0.75 mgs per mL to 150 plus or minus 22.5 mgs per mL of VEGF antagonist, right?
A. Correct.
Q. Okay.
And you didn't point that out in paragraph 205, right?
A. I didn't -- I didn't point what out?
Q. You didn't cite to that disclosure of Vitti in your declaration, right?
A. Point me in my declaration what you're referring me to. I'm lost here document-wise.
Q. Okay. So I'm --
A. What number are you in my declaration?
Q. Paragraph 205 of your declaration.
A. Okay.
Q. And I'm noting that you quote the language "may comprise 10 plus or

minus 1.5 mgs per mL to 100 plus or minus 15 mgs per mL of VEGF antagonist."

Do you see that?

A. Yes.

Q. Okay. And my question is very simple.

You do not also quote the language "5 plus or minus 0.75 mgs per mL to 150 plus or minus 22.5 mgs per mL of VEGF antagonist," right?

A. Yes. I saw no need to do so.

Q. Okay.

Why not?

A. Because I was quoting -- I was basing on the Australian label for a dose of 8 milligrams and I looked at a concentration of 115 milligrams per mL. There are vast range of concentrations offered in Vitti, but that seemed like a -- a reasonable injection volume. When I did my calculations, it came out to 70 microliters, and it seemed also a potentially doable target for my part of the team who was a co-formulation -- formulation expert. So that's why I

selected it.

I did not feel obliged to include the entire range of -- of numbers offered within the Vitti patent.

Q. Okay.

So when you say that 115 mgs per mL is the upper limit of Vitti's disclosure, you're leaving out the 150 plus or minus 22.5 mgs per mL, right?

A. Where do I say it's the upper limit?

Q. You say -- I'm sorry, you say it's near the upper limit.

A. Yeah, I don't say it's the upper limit.

Q. Okay.

So, when you say 115 mgs per mL is near the upper limit, do you view 115 mgs per mL as near an upper limit of, what is that, 172.5 mgs per mL?

A. Well, because of viscosity considerations are also going to enter into my mind, yes. I think that that's something that is -- is a very, very high concentration and unliable to be made. So

115 milligrams per mL seems to me to be a target concentration that a fabrication chemist can make.

Q. Okay.

So, you're not a formulator, right?

A. Right.

Q. And you don't know what concentrations formulators can make and what they can't, right?

A. I have an idea.

Q. You have an idea, okay.

So, you decided that a formulator could make a dis -- a formulation containing 115 mgs per mL of a VEGF antagonist, but could not make a formulation containing 172.5 mgs per mL of a VEGF antagonist?

A. Yeah, I think that's quite reasonable in my experience. I'm unaware of, you know, drugs that are formulated to that -- high protein drugs that are formulated to that high a concentration that can go through a 31-gauge needle. There are drugs that can probably be

formulated to that, but they would either be baths or emulsions or something like that, but not something that could be injected at a reasonable viscosity.

Q. Okay.

How are VEGF antagonists dosed?

A. Be more specific. You mean by intravitreal injection, by milligrams, by volume?

Q. I'm asking what's the route? Intravitreal injection?

A. Yes.

Q. Okay.

So, when Vitti refers to 150 mgs plus or minus 22.5, mgs per mL of VEGF antagonist, he means for intravitreal injection, right?

A. I'd have to review. I believe so.

Yes, he's discussing it in the context of intravitreal -- you're back to 93, I believe, is that right? 90 -- 94.

Yes.

Q. No, I'm talking about paragraph 87.

When Vitti discloses 172.5 mgs per mL of VEGF antagonist, he's describing a formulation for intravitreal injection, right?

MS. CHACON: Objection; vague.

A. Vitti is describing in 87 -- there -- there's no mention of route of administration of these agents.

Q. Okay.

Vitti does not mention route of administration in paragraph 94 either, right?

A. No. But it's clear that Vitti is describing a co-formulation or co-administration of two intravitreal agents. Paragraph 92 describes that pro -- process. Paragraph 93 goes in detail for the formulation of the anti-ANG2. Paragraph 93 -- excuse me, 94 describes the anti-VEGF aflibercept, and paragraph 95 now goes on to describe co-formulation of those agents.

Q. Okay.

A. I think a person of ordinary skill of the art would have no confusion

reading those paragraphs in the sequence that they have been outlined.

Q. Right.

And the person of ordinary skill in the art would have no confusion that par -- Vitti's disclosure -- in your opinion, Vitti's disclosure of formulation concentrations of VEGF antagonists were VEGF antagonists for intravitreal injection?

A. Correct.

Q. Okay.

Can you turn to example 7 of Vitti, which begins at paragraph 197?

A. Is it after all the -- oh, here. Yes, I'm there.

Q. Okay.

This is where Vitti starts discussing formulations by include -- examples of formulation that include aflibercept, right?

A. Yes.

Q. Okay.

And if you look at the examples written out in example 7 and then provided

in the tables that follow, am I correct that every example of an aflibercept formulation is formulated at 40 mgs per mL?

A. I would have to study these tables. These tables are dense, and I would have to review them in detail.

I'm happy to provide that.

Now, your question is are these all 40 milligram per mL tables?

Q. Well, maybe my better question is did you review these examples in forming your opinion about the concentrations of VEGF antagonist formulations that Vitti discloses?

A. I reviewed the Vitti patent, yes.

Q. Okay.

Sitting here today, do you know whether there are any working examples other than 40 milligram per milliliter of aflibercept in the Vitti patent?

MS. CHACON: Objection; vague.

A. I don't know of other examples.

The fact that he uses the word "example" means that there are other --

other concentrations and other formulations. He selected one. I'm not privy to his internal decision-making as to why he selected the example that he did, but certainly there were others.

Q. Okay. And -- sorry, can you turn back to paragraph 87 for me?

I just want to make sure I understand in reviewing Vitti's disclosure, you -- you started your analysis at the 10 to 100 plus or minus 15 mgs per mL --

A. Yes.

Q. -- disclosure. You, kind of, crossed out the first -- the 5 to 150 disclosure, right?

A. Well, the fact that a broader range is indicated, does not, as I understand it, disqualify a teaching from being obvious.

So, I had no need for it because I felt it might be -- the extremes would either be too difficult to formulate or would require too much injection volume. So I made a choice as disclosed for 115

milligrams per mL.

Q. Okay.

And you just saw no need to consider that line 5 to 150?

A. Well, I considered it, but I -- my understanding is that patents are generally written to provide as broad a range as possible for the patentholder. But I was interested in a target dose of -- a target dose of 8 milligrams as indicated by the Australian label, and Vitti signals in this later item 94 on a concentration of 100 plus or minus 15, and I took that piece of teaching as my target. So the -- the broad ranges described here are wonderful, but they didn't influence the fact that I already had a -- an understanding of the choice I wanted to make.

Q. And that was because you had already decided on a hundred -- sorry. You had already stated on 8 milligrams and 70 microliters?

A. I had already decided on 8 milligrams. Vitti teaches that this can

be done in a volume of approximately 70 microliters at a concentration of 115 milligrams per mL.

Q. Well, sorry. Vitti doesn't teach 70 microliters, right?

A. Vitti teaches 115 milligram per mL concentration in item 94, and if one has a target dose of 8 milligrams and does the math, that comes out to, as I think I've said multiple times, approximately 70 microliters.

Q. Okay.

What evidence -- on what evidence did you base your assumption that 115 mgs per mL of an aflibercept formulation would be workable for intravitreal formulations but 150 mgs per mL would not be?

A. Well, when I saw the calculation resulted in approximately 70 microliters and I knew that we had commercial products that went up to 90 microliters, and that the formulation would -- that typical products are in the 50 microliter range, 70 microliters is -- gives the formulation

chemist substantial latitude and they can try to formulate it at that, and that gives me also latitude as a treating physician and person of ordinary skill of the art to have a reasonable expectation that I can have a successful intravitreal therapy of 8 milligrams at the calculated 70 microliter injectate volume.

Q. Okay.

But if you had used 150 mgs per mL of a VEGF antagonist, you would have been able to use an even smaller volume, right?

A. If I used a lower concentration, I would need a larger volume.

Q. Okay. But my question was if you used 150 mgs per mL of a VEGF antagonist, you would have been able to use a smaller injection volume, right?

A. If -- if such were possible, yes.

Q. Okay.

And you don't have any opinion about whether such is or isn't possible, right?

A. I -- as I said, I keyed on a specific target as -- as available in the teachings of Vitti and the Australian label and Larson and selected a goal which I then discussed with the formulation chemist.

Q. Okay.

And that goal was 8 milligrams, right?

A. Correct.

Q. Okay.

And that goal was 70 microliters?

A. The goal was 8 milligrams, and then I looked to Vitti's teaching at -- okay, I'll say it again. I looked to Vitti's teaching of 115 milligrams per mL, and therefore the calculations suggest that 70 microliters, and that is a dose below the 90 microliters for Macugen. It's a dose above the 50 that many products have, but it is not an unreasonable dose as a starting point combined with needing to achieve an acceptable viscosity for administration

through a 30-gauge needle without elevating unduly the intraocular pressure of a patient.

Q. Okay. And I guess I'm just trying to understand why if Vitti also discloses 150 mgs per mL of VEGF antagonist formulations you didn't -- you wouldn't have pursued such formulations in order to get an even small injection volume.

MS. CHACON: Objection; asked and answered.

A. Yeah, and a -- a chemist would be the one -- a chemist would appreciate -- a chemist normally wants to have a higher volume, an injector wants to have a lower volume, and starting at the starting point in the middle, somewhere in the middle is the most -- is the most optimum place to begin drug development, in my opinion as a person of ordinary skill of the art with a reasonable expectation that that will be successful.

Q. Okay.

But you've never formulated an

intravitreal drug, right?

A. No.

Q. Okay.

So you just picked one of these ranges?

MS. CHACON: Objection; mischaracterizes testimony.

A. Yeah, you're -- you're character -- I think I'll say it again. I was guided by the Australian patent to seek a dose of 8 milligrams. I was taught by the Vitti patent that 115 milligrams per mL was a formulation of aflibercept. I then calculated that that would result in a volume of approximately 70 microliters. That is an acceptable volume within the range for intravitreal injection in patients. I then selected that volume because to go higher would give me a higher chance of pressure spikes in patients, and to go lower would make the job tougher on the formulation chemist. Which is well-known, I think is very clear the smaller, the more concentrated will have more problems

with -- with formulation. Therefore, the starting point was selected as 70 microliters with an 8 milligram dose.

Q. Let's take a look at a different exhibit. Exhibit 1009.

Dr. D'Amico, do you recognize this document?

A. I recognize it. I -- it's -- yes, I recognize it. It is a dense document, and I would need memory refreshed to review specifics, but I am familiar with the document.

Q. Okay.

And this was a document you found when you were searching for 8 milligrams of aflibercept, right?

A. This is a document that I am familiar with. I found it, yes, as part of this effort, yes.

Q. Okay.

As part of a effort to see whether 8 milligrams had been disclosed in the prior art?

MS. CHACON: Objection; mischaracterizes testimony.

A. Yeah, you -- yeah, you characterized my motivation for it.

I was involved in an effort to base -- to see whether certain aspects of 8 milligram dose were obvious, and this was part of the document search that I performed, yes.

Q. Okay.

Do you recall whether you put "8 milligrams" into Google?

A. I don't recall.

Q. Probably?

A. Probably not.

Q. Okay.

And can we turn -- what -- what dose does this label recommend that the skilled person administer of aflibercept?

A. Can you point me to the -- first of all, what is -- can you point me to the item in the document that you're referring to?

Q. Well, I'm asking you. You've reviewed this document.

What dose does it tell the skilled person to administer?

A. I would have to read the document. As I said, I would need memory refreshed.

So, let's see here.

I see from the table that it's referring to a 2 milligram dose of Eylea, aflibercept.

Q. Okay.

A. I'm not sure that's the only dose that's mentioned in this document, but I see it's a 2 milligram dose.

Q. Okay.

And if you turn to, for instance, page 29 of the document, you see the recommended dose for Eylea is 2 mgs of aflibercept equivalent to an injection volume of 50 microliters, right?

A. This is on page what?

Q. 29.

A. The recommended -- yes, I see that.

Q. Okay.

And so, the skilled person reading this document would have been motivated to administer a 25 milligram

dose of aflibercept in an injection volume of --

A. Yes.

Q. -- 50 microliters.

Okay. You suggest in your report that -- let me get back to the right page here. I'm looking at paragraph 43 of your report.

A. Okay.

Q. You say: Clinical trials also supported that there was no likely risk of drug toxicity with increasing dose of aflibercept to 8 milligrams.

Do you see that?

A. Yes.

Q. Okay.

What are you referring to there?

A. Clinical trials of aflibercept.

Q. Okay.

So Exhibit 1058 is -- contains clinical trials of aflibercept?

A. Let -- I'd have to review Exhibit 1058.

Q. Okay.

A. And that refers to my

declaration?

Q. 1058 is an exhibit, right?

A. 1058 is, yes, the European Medicines -- the EMA assessment of -- in September 12th, 2012.

MS. KAYALI: Okay. Let's mark this. That's 1058.

MS. CHACON: Counsel, do you want him to keep the --

THE WITNESS: Did you have this?

MS. KAYALI: It's up to him.

(Pause.)

MS. KAYALI: It's already marked.

BY MS. KAYALI:

Q. And you state that Exhibit 1058 at pages 20 through 21 have clinical trials showing that there was no likely risk of drug toxicity with increasing the dose of aflibercept up to 8 milligrams, right?

A. I'll find it and answer shortly.

It's on -- 20 describes monkey studies. Is that where you are in this document?

Q. Well, I'm just looking at where you point to the -- in your declaration?
A. What number in my declaration?
Q. So, I'm looking at paragraph 43?
A. 43.
Q. And do you see the sentence that says: Clinical trials also supported that there was no likely risk of drug toxicity with increasing dose of aflibercept to 8 milligrams.
Do you see that?
A. Yes.
Q. Okay. And that's an important feature of your opinion, right, because the skilled person wouldn't have been motivated to administer 8 milligrams if the skilled person thought it was going to be unsafe, right?
MS. CHACON: Objection; vague; calls for speculation.
A. Yeah, I mean, if a -- if a person thought a drug was unsafe, it goes without saying that one would not administer that medication.
Q. Okay.

And so you -- your testimony in your declaration was that clinical trials supported that there was no likely risk of drug toxicity with increasing the dose of aflibercept to 8 milligrams, right?

A. Yes.

Q. And the evidence on which you relied for that statement is at Exhibit 1058 at 20 to 21?

A. No, not the sole evidence. I also relied on the evidence of the Australian label which showed that doses of up to 8 milligrams -- or isolated cases were also well tolerated, and somewhere buried in these documents is a single dose of 20 milligrams which also after dealing with the massive intraocular pressure that I'm sure that patient sustained also did not have toxic effects.

So in part, yes.

Q. Okay. Much simpler question.

In paragraph 43 the only evidence to which you direct the board for your statement that clinical trials also supported that there was no likely risk of

drug toxicity with increasing the dose of aflibercept to 8 milligrams is Exhibit 1058 at 20 to 21, right?

MS. CHACON: Objection; mischaracterizes testimony and report.

A. Yes, that's a correct reading of my --

Q. Okay.

But it is not correct, right, that Exhibit 1058 at pages 20 to 21 discuss clinical trials, right?

A. That is correct. They discuss animal -- animal trials.

Q. Okay.

So, was your goal here -- I mean, would you like to withdraw that statement from your declaration?

A. I think the statement is -- I would like to withdraw the word "clinical trials."

I would say that the statement should be "experimental trials."

Q. Okay.

So this statement accidentally conveyed to the board that there was

better evidence for your opinion than you actually have in Exhibit 1058, right?

MS. CHACON: Objection; mischaracterizes testimony; argumentative.

A. Yes.

Q. Okay.

Then can you look at the sentence right before that: As it relates to the issues I have been asked to opine on, these clinical trials demonstrate that increasing the dose of aflibercept would prolong its duration of action in the eye resulting in a reduction in the frequency of injections for patients.

Right?

A. Yes.

Q. Okay.

Again, that's another, sort of, linchpin of your opinion. You wouldn't want to give higher dose aflibercept unless you thought either it was going to be more effective or last longer, right?

A. I -- I'm lost here. Hold on.

You're saying that you wouldn't

want to give --

Q. Well, let me ask a different question.

Your opinion in this case that the claims of Regeneron's patents would have been obvious turn on your opinion that the skilled person would have wanted to administer a higher dose of aflibercept in order to achieve either better efficacy or a longer duration of action, right?

A. The field would wanted higher -- higher efficacy or longer duration of action, that is correct.

Q. Okay.

A. As evidenced by multiple pieces of data that we've discussed, such as the Harbor Trial.

Q. Okay.

And for that proposition, you cite Exhibit 1039, right?

A. Yes.

Q. Okay.

I think you have 1039 buried in there somewhere. Can you --

A. What is 1039?

Q. I think it's the Stewart paper.
A. Okay.
Q. Okay.
And you're relying on Exhibit 1039 at 1182, right?
A. Yes.
Q. Okay.
And when you say in your declaration, you say: These clinical trials demonstrate that increasing the dose of aflibercept would prolong its duration of action in the eye resulting in a reduction of the frequency of injections for patients.
Right?
A. Yes.
Q. Okay.
And so you're telling the board that you're going to point them to clinical trials for aflibercept, right?
A. Hold on.
Aflibercept -- Stewart relates to not only aflibercept, but other trials as well. But yes.
Q. Okay.

But in paragraph 43 you're telling the board --

A. Yes.

Q. -- you're talking about it for the purpose of aflibercept, right?

A. Yes.

Q. And you're talking about aflibercept trials?

A. Right.

Q. And so the aflibercept trial that Dr. Stewart references there is the VIEW trials?

A. Yes.

Q. Okay.

Can you -- did you -- let's see. Okay.

And the sole piece of data relating to aflibercept in this paragraph is the VIEW trial showed that aflibercept 2 milligrams every eight weeks produced vision gains comparable with the aflibercept 0.5 mgs every four weeks.

Right?

A. No. The next paragraph top of column 2: Both trials suggest, but do not

prove, that increasing the dose of the drug prolongs its duration of act -- of action.

Q. Okay.

And when you say "both trials," what -- what Stewart is talking about there is the VIEW trials and Harbor, right?

A. Correct.

Q. Okay.

Only the VIEW trial relates to aflibercept, right?

A. Right.

Q. Okay.

So you're talking about one clinical study for aflibercept and a separate clinical study --

A. Right.

Q. -- for ranibizumab?

A. Yes, both trials.

Q. Okay.

Can you take a look at paragraph 12 of your declaration?

Okay. And you've got that table of materials you considered there?

Where did you consider the data for the VIEW trial?

A. I considered the VIEW -- I considered the VIEW trials to be embodied in the knowledge of a person of ordinary skill in the art.

Q. So you didn't go back and look at the data for the VIEW trials in forming your opinion?

A. I may have. I used the drug, so I'm quite familiar with it and quite familiar with its presentation and the studies that established its FDA approval.

Q. Okay.

You're familiar with the studies, but for -- in relying on the results of the studies, you only cite Stewart, right? You don't ever cite the -- the full data for the VIEW trials?

A. I didn't cite, but certainly whether I reviewed it or not over the last, you know, period of preparation, it's probable that I did, but I don't recall specifically the date or time that I performed that review because it's

something that I know well.

Q. Okay.

But you -- sitting here today, what are the other results that Stewart doesn't report of the VIEW trials?

A. What are -- you -- of two registration trials you'd like me to recount all of the results?

I don't understand your question.

Q. I'm asking why -- let me just ask a much simpler question.

In forming your opinions on this case, you do not cite the investigator's publication of the VIEW clinical trial data, right?

A. That's correct.

Q. Okay.

And then you go on to talk about Harbor, right?

A. Yes.

Q. And then you say: These results are consistent with --

A. What paragraph are you in?

Q. I'm in Stewart.

A. You're still in Stewart, okay.
Q. Yep. Do you see at the bottom of the paragraph we have just been looking at you say: These results are consistent with previously published models which predict that increasing the dose of an effective anti-VEGF drug has a greater effect on its durability than its efficacy.
Right?
A. Yes, and that was -- that was the understandings of a person of ordinary skill of the art at the time.
Q. Okay. And you cite that statement throughout your declaration, right?
A. That is correct.
Q. Okay.
It's an important statement, from your perspective?
A. It's one of many pieces of important information in my declaration.
Q. Okay.
What do those models show?
A. That there were no harmful

effects from going to higher dosage, that it may have an effect -- and in clinical trial with -- with ranibizumab, it did have an effect on prolonging duration, but the prediction is that whatever work VEGF is doing in terms of reducing fluid and improving visual acuity, it's probably reached its efficacy peak but not its duration peak.

Q. So, sorry, when you say "previously -- these results are consistent with previously published models which predict that increasing the dose in effective anti-VEGF drug had a greater effect on durability than and efficacy," and then you cite -- Stewart is citing reference 114, are you saying these previously published models reflect clinical trials?

A. No. These are -- these are pharmacokinetic studies of intravitreal injection of drug.

Q. Okay.

And can you turn to reference 114?

A. Yes.
Q. What is that paper?
A. Preclinical. So that would mean prior to human studies, pharmacokinetics of ranibizumab after a single intravitreal injection.
Q. Okay.
And if you look in paragraph 12 of your materials considered, you must have reviewed these models to rely on them, right?
A. I'm aware of the studies, yes.
Q. Okay.
But where in your materials considered did you say that you relied on the Gaudreault reference?
A. I don't believe I referenced Gaudreault specifically.
I referenced Stewart.
Q. Right.
But for a statement you cite, I don't know, half a dozen times in your report, that published models predict that increasing the dose of effective anti-VEGF drug has a greater effect on its

durability than its efficacy, I think what you're saying is you did not separately go back and review the Gaudreault paper, right?

MS. CHACON: Objection; mischaracterizes his testimony.

BY MS. KAYALI:

Q. You took -- you took Stewart's summary at its face value?

A. I took Stewart's peer-reviewed article as indicative of the understanding at the time that was widespread to a person of skill of the art that the VEGF effect on efficacy was probably at a ceiling, but durability was still looking promising with higher doses, yes. And I relied on Stewart to -- who reviewed that in -- in the peer-reviewed literature.

Q. Okay.

So you're not familiar sitting here today with the ins and outs of those models?

A. I'm familiar with pre -- preclinical drug studies.

So please specify what aspects I

may or may not be familiar with.

Q. I'm not asking about them in general. So I suppose we can move on.

I'm asking -- well, nothing.

MS. KAYALI: Strike that.

Q. Okay. So, going back to paragraph 43 of your declaration. I think we were looking at -- you said: I have been asked to opine on these clinical trials demonstrate that increasing the dose of aflibercept would prolong its duration of action in the eye resulting in a reduction of the frequency of injections for patients.

Right?

A. Right.

Q. "Demonstrate," that means to you what?

A. What does the word "demonstrate" mean?

Q. What did you mean it to -- to mean in paragraph 43?

A. I meant that the prevailing understanding was that increasing the dose would prolong the duration of -- of action

and that therefore it would lead to a reduction in the need for frequent injections in patients.

Q. Where do you talk about the prevailing understanding?

You just mentioned that the clinical trials demonstrate that increasing the dose of aflibercept would prolong its duration of action, right?

A. Right.

Q. Stewart says instead: Both trials suggest but do not prove that increasing the dose of a drug prolongs its duration of action.

Right?

A. Yeah, I take that as permissive. They suggest but do not prove. Maybe an even higher dose needs to be studied. Maybe more patients need to be studied, but it certainly is not a discouragement to study high doses.

Q. Okay.

But they don't actually demonstrate that increasing the dose of aflibercept would prolong its duration,

right?
A. They suggest that it does. They don't demonstrate it.
Q. Okay.
So you would revise the statement in paragraph 43 of your declaration to change the word "demonstrate"? You would take out the word "demonstrate"?
A. I'm trying to find out where the word "demonstrate" --
Q. Bottom of the page. You see it?
A. Yes.
Q. Okay.
So you'd revise actually both -- you -- neither sentence in paragraph 43 is -- is perfectly accurate?
A. That is correct.
Q. Okay.
You accidentally implied to the board that you had more evidence for your position than you did in both cases?
MS. CHACON: Objection; mischaracterizes testimony.
A. The statements are -- the

statements are inaccurate as written.

Q. Okay.

In paragraph 45, we -- I think we already talked about 45. We talked about CLEAR-IT 1, and then you go on to talk about CLEAR-IT 2.

I just want to make sure I understand every citation you have to CLEAR-IT 2 in your declaration is -- or at least let's start with in paragraph 45 is Exhibit 1039 which is Stewart, right?

A. Which is Stewart. Yes, that's correct.

Q. Okay.

So you don't separately cite the investigator's publication of CLEAR-IT 2?

A. No.

MS. CHACON: Objection; asked and answered.

BY MS. KAYALI:

Q. Okay. Let's take a quick look at Exhibit --

(Pause.)

Sorry. 1026. This has already been marked.

Are you familiar with this paper?

A. I am.

Q. When was the last time you looked at it?

A. A few days ago, within the last four days.

Q. Okay.

And, okay. Can you take a look at page 10 of Exhibit 1026 for me, please?

A. Yes.

Q. Okay.

And do you see the paragraph beginning "In conclusion" there?

A. Yes.

Q. Okay.

So, the authors of Ho published in 2014, which is the 24-month efficacy and safety of a ranibizumab study --

MS. KAYALI: Well, strike that.

Q. Ex -- the authors --

MS. KAYALI: Strike that.

It's been a long day.

Q. The investigators of the Harbor study state in Ho, published in 2014,

that: In conclusion, the Harbor two-year results demonstrate that all four ranibizumab groups maintained their visual and anatomic improvements on average between months 12 and 24 of the study.

Do you see that?

A. Yes.

Q. Okay.

And you agree with that?

A. Yes.

Q. Okay.

Now, the next sentence reads: Over two years, the 2 milligram dose did not show any cleaning -- clinically meaningful difference in efficacy, durability, or safety compared with the 5 milligram ranibizumab dose.

Right?

A. Yes.

Q. Okay.

And you agree with that?

A. Yes.

Q. Okay.

I'm sorry, I may have misspoke.

The sentence reads: Over two

years, the 2.0 milligram dose did not show any clinically meaningful difference in efficacy, durability, or safety compared with the 0.5 milligram ranibizumab dose.

Right?

A. Yes.

Q. Okay.

And you agree with that?

A. Yes.

Q. Okay.

Can you take a look at paragraph 166 of your declaration?

A. I'm there.

Q. You say: High doses of aflibercept and other similar proteins would be something a POSA would be interested in. The field was investigating ways to reduce the frequency of administration by increasing the dosage.

Then you cite Stewart at 1183.

Studies showed that decreases the number of intravitreal injections decreases cumulative incidents of ocular complication.

And then you cite Exhibit 1026 at 1.

Comparing 0.5 and 2 milligrams of ranibizumab with results showing increased dosage of anti-VEGF drug has a greater effect on durability than efficacy and no -- showing no new safety events with [inaudible].

Right?

A. Yes.

Q. Okay.

When you compare your statement regarding Harbor, you say: Harbor study had results showing increased dosage of anti-VEGF drug has greater effect on durable than efficacy.

Right?

A. Yes.

Q. How does that compare to the statement "The 2 milligram dose did not show any meaningful difference in efficacy, durability, or safety"?

A. The word "clinically meaningful." As it's -- as the authors state, efficacy was the same, the safety

was the same. The PRN group with the higher dose required few injections per year.

Q. Okay.

A. So therefore, in all comparisons, the 4 milligram dose was either equal or superior.

It was not clinically meaningful in order for Genentech to make a new drug and spend 800 million, but if they had marketed the 4 milligram first and offered this data to the person of ordinary skill in the art, a person of ordinary skill in the art would have selected the 4 milligram -- excuse me, the 2 milligram dose because it had only equivalence or a trend toward an advantage.

So I don't see -- I don't see any contradiction between "clinically meaningful" and the statement that it was -- you know, it was either equivalent or trending better than the low dose.

Q. Okay.

A. That's how I resolve that con -- that question that you've asked.

Q. When did you be -- first become aware of the need to resolve that question?

A. I have been aware of the Harbor study and have presented on the Harbor study at meetings. I'm intimately familiar with the data.

Q. Okay.

And you stand by your statement that increased dosage of anti-VEGF drug, meaning ranibizumab, has a greater effect of durability than efficacy, that that's what Exhibit 1026 shows?

A. Yes.

Q. Okay.

And you stand by that notwithstanding the fact that the authors concluded the 2 milligram dose did not show any clinically meaningful difference in efficacy, durability, or safety, right?

A. The phrase "greater effect" is correct, and "clinically meaningful" is a highly limiting phrase. It's not -- it was no difference, a clinically meaningful difference, and I take that to mean

something that would be meaningful to a clinician. It does not imply that they're not different. It implies the difference was not significant enough for them to pursue marketing a new drug.

Q. Okay.

Where in your declaration do you explain to the board what the authors of the Harbor study concluded?

A. I'd have to review where -- let's look at the table of contents and see.

I -- this is certainly one place, 166.

Q. So, maybe I have a better question.

Do -- anywhere in your declaration, do you recall, sitting here now, pointing the board to the language that we just discussed "over 2 years the 2 milligram dose did not show any clinically meaningful difference in efficacy, durability, or safety"?

A. I -- I reference the Harbor study in my declaration. So I don't -- I

don't understand your question, I guess is what I'm saying.

Q. Okay.

A. I think that the assertion that it -- it had a greater effect on durability than efficacy and showing no new safety events is accurate and adequately referenced in my declaration.

Q. Notwithstanding the author's conclusion to the contrary?

A. Not -- the authors did not conclude to the contrary. The authors concluded it was not clinically significant.

Q. Okay.

A. They did not dispute a difference, and that's very clear by the fact that they also mention that fewer injections were re -- were required at higher dosage.

Q. Okay. Let's go back to Exhibit 1009.

A. What is that exhibit? Do I have it already?

Q. You do. It's the Australian

label.

Okay. Can you look at page 35?

A. I'm there.

Q. You're already at page 35.

A. Had a hunch.

Q. You had a hunch I was going to ask you about the overdosage section?

A. Yes.

Q. Okay.

And that's because you rely on the overdosage section of this Australian label to support your opinion that the skilled person would have been motivated to use a dose of aflibercept that is 8 milligrams, right?

A. Correct.

Q. Okay.

And your basis for that is that there were clinical trial doses of up to 4 milligrams in monthly intervals, right?

A. Yes.

Q. And you say: Isolated cases of overdoses -- excuse me.

The label says: Isolated cases of overdoses with 8 milligrams were

generally well tolerated.

Right?

A. Yes.

Q. And it's only the second part of that, "Isolated cases of overdoses with 8 milligrams were generally well tolerated," that would motivate the skilled person to use a dose of 8 milligrams, right?

A. No.

MS. CHACON: Objection; mischaracterizes.

Go ahead.

A. Yeah, no. The entire first sentence is under the heading of "Overdosage." So one could also say that in the characterization here that 4 milligrams is an overdosage because the label is describing a 2 milligram dose of aflibercept.

Q. Okay.

There was some clinical trials, though, that evaluated 4 milligrams of aflibercept, right?

A. That's correct. That's correct.

Q. Okay.

And do you know whether the isolated cases of overdose that led to 8 milligrams occurred because there were, like, a double injection of a 4 milligram or a quadruple injection of a 2 milligram dose?

A. I do not have that information.

Q. Okay.

So you don't know the volume that was injected into these patients, right?

A. I suspect it was high because, you know, they talked about intraocular pressure issues, but whether they had them or not in these specific patients is not determinable from the materials in front of me.

Q. Okay.

So you don't know whether they dosed two times 4 and therefore maybe -- I don't know, but maybe a hundred microliters or four times 2 which would be 200 microliters?

A. I think the volume would be the

same. They had a certain formulation in front of them which was undoubtedly 40 milligrams per mL, and therefore the only thing that would have been different would be the -- would be the -- the volume.

Q. Well, do you know that that's the formulation used in the 4 milligram studies?

A. Again, isolated cases of 8 milligram overdoses. I do not know that, no.

Q. Okay.

And you -- how many publications reproduced the result described in this -- on page 35 of Exhibit 1009?

A. How many publications reproduced what result?

Q. The -- how many clinical -- excuse me, publications reproduced the result that overdoses of 8 milligrams were generally well tolerated?

A. I think this is the only one.

Q. Okay.

And isolated cases, that means, what, at least?

A. At least two.
Q. Okay.
But you don't know if it was any more than that?
A. No.
Q. As a matter of fact, you and the POSA and any member of the public, this is the sum total of information they have about the 8 milligram overdoses, right?
MS. CHACON: Objection.
A. There's also information about a 20 milligram --
(Stenographer instruction on cross talk.)
MS. CHACON: Objection; calls for speculation.
Go ahead.
A. There's also information available about a 20 milligram dose in the literature.
Q. Okay.
But you ignored that one for purposes of selecting a dose and you picked 8 milligrams, right?
A. Correct.

Q. All right.
A. For the reasons that I previously outlined.
Q. Because you -- why, because you only had to get to 8?
A. The next logical dose escalation is four times the prior dose, and given an initial approved dose of 4, the next logical dose would be 8 milligrams. One would be looking -- a person of ordinary skill of the art would be looking to see if there's any information available about an 8 milligram dose of aflibercept.
Q. Okay.
And the information provided here is that at least 2 -- in at least two instances, 8 milligrams was generally well tolerated?
A. Yes.
Q. Okay.
And what does "generally well tolerated" mean? How did they assess that?
A. Pardon?
Q. There's no data here about how

the investigators assessed whether the overdoses were generally well tolerated, right?

A. They say they were generally well tolerated. They did not lose the eye. They did not have rip-roaring retinitis. They did not have vision decrease.

They described generally well tolerated, which I take and I think a person of ordinary skill of the art would take that there was no additional -- additional toxicity associated with that -- with that dose.

Q. Were there -- did Regeneron present subsequently on this finding that 8 milligram doses were generally well tolerated?

A. I'm not -- I'm not familiar with all of Regeneron's presentations, but they certainly -- there's certainly a publication here which was available that indicates an 8 milligram dose was generally well tolerated.

Q. Who administered the 8 milligram

dose?

A. The clinical trial described one can only impute or infer that it was a treating physician. I'm not familiar with procedures that were, you know, applied in these particular cases, but it would be a physician.

Q. Okay.

Do you know where that physician was located?

A. I do not.

Q. You don't know in which country?

A. I do not.

Q. Do you know if Regeneron did trials in Turkey?

A. I do not.

Q. Okay.

And what -- what data is presented for your consideration regarding the tolerance of the 8 milligram dose?

A. It is generally well tolerated.

Q. Okay.

So there's no data showing what effect it had. You just -- you're taking "generally well tolerated" is it, right?

A. In the same -- yes, in the same way that if I gave an overdose of a medication to a patient orally and said they were fine with no effects, generally well tolerated, I think that is -- is inclusive and descriptive that there were no harmful effects noted in an environment where there was monitoring for -- monitoring for safety events. So a high level of data.

Q. This is -- this statement reflects a high level of data --

A. Correct.

Q. -- in your opinion?

A. To me, yes.

Q. Okay.

And do you know when in the clinical trial the patient was -- the patient or patients received an.

8 milligram dose erroneously?

A. No.

Q. Okay.

So, do you know how -- for how long that patient was followed after receiving the 8 milligram dose?

A. Well, in general principle, any patient enrolled in a registration trial or in a trial is followed for a long time through the conclusion of the trial.

Q. Okay.

But you don't know how close to the conclusion of the trial this 8 milligram dose was administered, right?

A. I have no idea.

Q. Okay.

So you don't know how much more monitoring they received, right?

A. Oh, I -- an overdosage of this nature, the patient would be closely monitored. Hence the statement "generally well tolerated."

Q. Okay.

You've been a clinical study investigator, right?

A. Yes.

Q. Sorry, let me ask a different question.

Do you know what happened, do you know how someone accidentally administered 8 milligrams?

A. I was not present. I have no idea how they did it.

Q. Okay.

And you don't know how they concluded later that they had administered 8 milligrams, right?

A. Again, I was not present. I have no idea how they did it.

Q. Okay.

So you don't know if they had some sort of dilution error or a double injection or -- or anything of the above, right?

A. I don't know.

I'm assuming that they had a -- or had access to the 2 milligram preparation and that, therefore, they administered four times the recommended volume. I -- I just infer that by the fact that they immediately start talking about increased intraocular pressure, et cetera, and -- and that's the -- the sole concern that they raise in their discussion, but I have no -- no information beyond the specifics provided

in this paragraph.

Q. Okay.

And as a clinical study investigator, let's say -- I understand you didn't do this, but I'm asking if you were in a clinical trial and you had made a mistake, you had given an overdose, you would report that to the study sponsor, right?

A. Yes. And there may be additional reporting to the FDA, et cetera, to local authorities. All sorts of things go on.

Q. Okay.

So, Regeneron would have known the details about how many cases of overdoses there were, what happened to those patients, for how long they were monitored, et cetera, right?

A. I would assume so, but I don't have that information. I'm not familiar with Australian -- Australian law.

This -- this label creation in the United States is a highly specific thing that requires extensive interaction

with the FDA and other agencies. I'm not familiar with Australian law in the least, but I would assume that the sponsor company would know -- have more information about this.

Q. What does the Australian label for Lucentis say?

A. I do not know.

Q. Okay.

Do you normally look at Australian labels?

A. No.

Q. Okay.

Did you identify the Australian label, or did counsel provide it to you?

A. Counsel provided it to me.

Q. Okay. Let's take a look -- you can put that aside.

MS. KAYALI: Let's take a quick break, because I think our next session will be our last, and that way I can get my ducks in a row.

THE WITNESS: Okay. Great.

THE VIDEOGRAPHER: The time right now is 5:00 p.m., and we are off

the record.

(Recess taken.)

- - -

E V E N I N G S E S S I O N

- - -

THE VIDEOGRAPHER: The time right now is 5:29 p.m., and we're back on the record.

BY MS. KAYALI:

Q. Okay. Can you turn to paragraph 169 of your declaration?

A. 59 or 69?

Q. One-six-nine, please.

A. I'm there.

Q. Okay.

And you say, the last sentence of that paragraph you say: A POSA would have had -- would also have had a reasonable expectation of success in increasing the dose of low dose Eylea 2 mgs flow forth from the Harbor study which demonstrated a four time dose of ranibizumab was tolerated efficacious and

had increased durability.

Do you see that?

A. I'm at the last paragraph. It says -- I don't see "durable," et cetera.

I have "a POSA would have a reasonable expectation" in 169 "in targeting"?

Q. I'm looking at the last sentence of that paragraph, which is on the next page.

A. Oh, okay. Sorry.

Q. That's okay.

Do you see the sentence I just read?

A. Yes.

Q. Okay.

And so, in that instance, you're extrapolating from what the Harbor study showed about ranibizumab to what a POSA, in your opinion, might expect about aflibercept, right?

A. Yes.

Q. In forming that opinion, it would be important to consider whether there are any differences in safety

among -- between ranibizumab and aflibercept, right?

MS. CHACON: Objection; vague.

A. Between ranibizumab and aflibercept, not necessarily. It would be important to consider whether there were any differences in safety between the 0.5 milligram dose of ranibizumab and the 2 milligram dose of ranibizumab, but again, every drug needs to be studied on its own basis, and I don't see that -- you know, that differences in safety would necessarily be extrapable from one -- if that's a word, from one drug to another.

Q. Okay.

And nor would differences in efficacy, right?

A. Correct.

Q. Okay.

And so, the ability to extrapolate from data for ranibizumab to data for aflibercept --

MS. KAYALI: Strike that.

Q. Are you aware of any study comparing the safety of various

concentrations of aflibercept and ranibizumab?

MS. CHACON: Objection; vague.

A. I'm aware of a study, the VIEW trials compared doses of ranibizumab versus -- doses of aflibercept versus a standard dose of ranibizumab. Not exactly what you're asking for, but that -- there is data like that in the VIEW trial.

Q. Okay.

And are you -- the VIEW trial compare -- the highest doses tested in the VIEW trial are 2 milligrams Eylea and 0.5 milligrams ranibizumab, right?

A. As I recall, yes.

Q. All right.

So, are you aware of any study comparing the safety of concentrations that exceed the clinical dose of aflibercept and ranibizumab?

MS. CHACON: Objection; vague.

MS. KAYALI: Let me try that again.

BY MS. KAYALI:

Q. Are you aware of any research

comparing the safety of -- of concentrations of aflibercept and ranibizumab that cor -- that -- that reflect greater than the approved clinical doses?

A. Of what?

Q. Aflibercept and ranibizumab.

A. I -- if I have referenced them in my paper, I would like to be pointed to them. They don't immediately come to mind.

Q. Okay. I -- I'm not aware that you've cited any.

I guess I'm just asking are -- are you aware of any?

A. I don't think so.

Q. Are you aware of any research comparing how high above the -- the clinical dose equivalent of ranibizumab you can go before you get toxicity versus how high above the clinical -- the normal clinical dose of 2 milligram aflibercept before you get toxicity?

MS. CHACON: Objection; vague.

A. Yeah, I --

MS. CHACON: Calls for speculation.

A. Yeah, I'm not aware of any.

I'm aware of studies that have looked at toxicity aflibercept in high doses in animals, rats and monkeys and things like that. I presume I have at some point in my career looked at similar studies for the much earlier ranibizumab, but a comparative dose escalating trial and establishing upper limits, I don't -- I'm not aware of that. And if I've cited it in my report, I would ask to be pointed to the appropriate section.

Q. I -- I'm not aware that you have cited it in your report.

I -- my question is maybe just you're not aware of any such research, but if it existed, it would be useful to consider in forming your opinions here, right?

A. I think that's doubly hypothetical. But, yes, if there were -- if there were -- answering a double hypothetical is always tricky. But, yes,

if such information existed, it would be one more element that would inform my decision.

Q. Okay.

Because if there were differences in the safety profile between ranibizumab and aflibercept, that would -- that would affect whether or not you can apply knowledge from increasing doses of ranibizumab to your expectation of increasing doses of aflibercept, right?

A. Not at all.

MS. CHACON: Objection; vague.

THE WITNESS: Sorry.

MS. CHACON: Go ahead.

A. Not at all. The drugs are different. So, the drugs are different. The -- the safety effects could be different. The effect of higher dosage could be different, et cetera.

It could be the same. It would be a piece of information. It could be the same, but your statement asks for an absolute which I'm incapable of giving.

Q. So it would be relevant?

A. All information that we've discussed would be relevant. Whether it would be enough to make the decision, but all the information we've been discussing would be relevant.

Q. Okay.

Can you turn, please, to -- actually, let's look at Exhibit 1010.

Okay. Do you recognize this document?

A. I do.

Q. When did you first see it?

A. When I began working on this project.

Q. Okay.

And did you find it, or was it provided to you by counsel?

A. It was provided to me by counsel.

Q. Okay.

What's the title of Larson in the upper left corner?

A. Want me to read it?

Q. Yes, please.

A. "Liquid protein formulations

containing water soluble organic dyes."

Q. Okay.

So, you reviewed Larson, right?

A. Yes.

Q. Okay.

Larson is directed to reducing the viscosity of formulations using water soluble dyes, right?

A. Adjusting. I'm not sure they're only reducing, but adjusting the viscosity using water soluble dyes, yes.

Q. Okay.

What's the -- as a treating clinician, why -- why do you care about viscosity?

A. Because I want to minimize the size of the needle through which I am injecting the drug, and I want to -- to make it comfortable for the patient administering with, for example, a transfusion of 16-gauge or 14-gauge transfusion needle into the eye would be ludicrous. Administering with a 43-gauge needle would be virtually impossible with almost any liquid. So I want to minimize

the discomfort to the patient.

I also want to control the volume of the injectate to minimize the intraocular pressure spike.

Q. I see. So, the more viscus the formulation the less able you are to control volume.

Is that what you're saying?

A. No. The more viscus the formulation, the more larger needle bore one would need to be able to force it through -- the needle to the eye. You'd have to use a bigger needle, and hence it would be more painful, and it would also potentially leave a -- a larger wound that can either become infected or leak.

Q. Okay.

And so it's the force required to push the drug through the needle that's, sort of, the limiting factor from a clinician's perspective?

A. And also the needle size, as I've mentioned.

Q. Sure.

So if you're holding the size of

the needle constant, you -- you want to use a particular needle, in your opinion, right?

A. Correct.

Q. And which one is that?

A. 30, 31-gauge.

30-gauge needle is standard, yes.

Q. Okay.

So there is, sort of, an upper limit to viscosity in which it is comfortable to push through a 30-gauge needle for you?

A. That is correct.

Q. Okay.

So, are you -- as viscosity goes up one unit -- what's the relationship between force and viscosity? Is it linear? Is it exponential? Do you know?

A. It's -- it's highly complex. It's measured in daltons, and it is one of the most complicated physical chemical measurements we make on a liquid.

It also depends on the length of a -- of a tube that it's going through.

So in other words, a half-inch needle will permit an easier injection at a given viscosity than will a 1-inch or will even a 2-inch needle.

So I can't, without more data and without being in a lab with an analytical chemist, provide more, but it's a highly -- it's an important and very complicated property of a liquid.

Q. Viscosity is?

A. Viscosity is.

Q. Okay.

And you -- you weren't the viscosity expert in this case. You -- Dr. Falconer was, right?

A. That is correct.

Q. Okay. And my question I think is simpler.

It sounds like what you care about as the clinician is how hard do I have to push down on the needle and can I use a 30-gauge?

A. Correct.

Q. Okay.

And I'm asking whether you know

how -- if you hold the size of the needle constant, whether the relationship between increasing viscosity and increasing force required is linear, exponential, logarithmic, or something else?

A. I don't -- I don't have that information.

Q. Okay.

So, you don't -- okay. Your -- so, if you look at the abstract of Larson, it says: Concentrated low viscosity. Low volume liquid pharmaceutical formulations of proteins have been developed. Such formulations can be rapidly and conveniently administered by subcutaneous or intramuscular injection rather than by lengthy intravenous infusion.

Right?

A. Right.

Q. Okay.

So, this reference is discussing taking a drug that's formulated for one method of administration and converting it to a different one, right?

MS. CHACON: Objection; vague.

A. Yes. The abstract describes the generalizability of formulation of low viscosity prot -- the low volume liquid protein formulations.

Q. Okay.

And it does so -- its discovery is that you can use water -- viscosity-lowering water soluble organic dyes.

Sorry, that was a mouthful. Let me try again.

The -- what Larson is conveying to the skilled person is that in order to reduce viscosity, you can use viscosity-lowering water soluble organic dyes, right?

A. Yes.

Q. Okay.

You don't offer the opinion in your declaration that the skilled person seeking to make an intravitreal formulation would have wanted to add viscosity-lowering water soluble organic dyes, right?

A. Again, in my declaration, I'm

part of a -- a POSA is described as part of a team, and that expertise is clearly within the range of the formulating chemists.

So, no, I don't believe I offer that. If I do, I would like to be pointed to the specific reference.

Q. Okay.

Are you in the habit of injecting dye into your patients' eyes with intravitreal injections?

A. Yes, we use organic and inorganic dyes in vitreoretinal surgery by injecting them intraocularly to stain tissues various colors to facilitate their visualization: indocyanine green, trypan blue, blue membrane blue, brilliant blue.

So, yes, those are used.

Q. Okay.

But you don't have a -- you're not aware of any intravitreal injection of an anti-VEGF agent that includes a dye, right?

A. I have no knowledge -- I have not read the formulation composition of

the available drugs that I'm using in my clinic, and I have no way, without -- without specific chemical knowledge, of knowing whether the existing formulations of Macugen, faricimab, Eylea, ranibizumab, or aflibercept incorporates some element of a chemical that might be termed an organic or inorganic dye. So I -- I can't answer the question without a precise chemical formulation.

I would assume that viscosity adjustments have been made to all of those agents in order to create an acceptable viscosity, but again, I can't prove that.

Q. Okay.

So you would just defer to Dr. Falconer on what excipients and active ingredients are suitable for intravitreal administration?

A. Yes, and as disclosed in Larson, we have an idea that organic -- I think he uses organic or inorganic -- that dyes can be used to adjust the viscosity of a -- of a protein formulation.

Q. Okay.

And you're aware that at Dr. Falconer's deposition, he testified under oath that Larson does not disclose any formulation suitable for intravitreal administration.

Are you aware of that?

A. I don't recall that. I may have read it, but I don't recall that specifically.

Q. Sorry.

Did you read his deposition testimony?

A. No, I did not read his deposition testimony.

Q. Okay.

So, Dr. Falconer, I'll represent to you, did testify and say Larson does not disclosure any formulations suitable for intravitreal administration.

And my question is simply you have no reason to disagree with Dr. Falconer on that point, right?

A. I -- again, I'm not sure how he arrived at that conclusion.

But the -- the Larson patent

describes precisely the opposite, the generalizability of low viscosity, low volume liquid formulations that instead of being administered intravenously can now be administered by subcutaneous or intramuscular injection.

But I will specify that his expertise in this area is greater than mine.

Q. Okay.

So, do you disagree or agree with Dr. Falconer's conclusion?

A. I have no reason to disagree with his conclusion, so I would agree with it.

Q. Okay.

Could you turn, please, to paragraph 292 of your declaration?

A. I'm there.

Q. Okay.

You state in paragraph 292 that: A POSA would also have understood that Fielder disclosed that a most preferable injection volume administered to the patient is 0.05 milliliters which equates

to 50 microliters.

Right?

A. Yes.

Q. Okay.

And that's a -- it says uL, but that should be the Greek U for microliters?

A. Where are you speaking?

Q. I'm looking at the third line of paragraph 292.

A. Oh, yeah, uL should be a Greek Mu.

Q. Mu, okay. I was looking for that. Thank you.

Okay. And you say that: The POSA would have understood that Fielder's disclosure of a preferred injection volume of 50 microliters is the same injection volume disclosed in the AU label.

Right?

A. Correct.

Q. Okay.

And you say also that: As charted above in Section V.E.1 a POSA would have further understood that other

intravitreal injections of VEGF antagonists use intravitreal injection volumes of 50 microliters.

Right?

A. Correct.

Q. Okay.

So this is an opinion that the skilled person would have been motivated to use a volume of 50 microliters?

MS. CHACON: Objection; mischaracterizes.

A. Yes. It's a -- it's certainly a target volume for intravitreal agents.

Q. Okay.

And then you're referring to a chart, and I just need to get back to where that is.

I think that -- I think chart you're referring to is in paragraph 72. Could you take a look, please?

A. I'm there.

Q. Okay.

These are the drugs and injection volumes that you took into account when considering whether the

skilled person would have been motivated to proceed as you've outlined, right?

A. Yes.

Q. Okay.

And you considered the -- the dose of those drugs, right?

A. I considered the dose and the injection volume, yes.

Q. Okay. For each of pegaptanib - I'll never get that right - ranibizumab, bevacizumab, aflibercept, brolucizumab and faricimab?

A. Yes.

Q. Okay.

Have you ever offered an opinion about whether or not some --

MS. KAYALI: Or, let me strike that.

Q. You testified earlier today that you hadn't been deposed, I believe, in a patent case before, but that you've had -- worked with someone in a patent case before, right?

A. That -- to my best -- I certainly worked in the, as you described

it, the Alcon case with a patent office, as I also mentioned, in Chicago. The case of, like all patent cases, took place over a lengthy period and was ultimately settled. I can't -- certainly I never went to trial. I can't -- I don't believe I was -- I'm pretty sure I was never deposed, but documents were certainly created and exchanged, and whether there were declarations or not I can't recall.

Q. Okay.

Do you recall whether any opinion you've ever offered in a proceeding was excluded by a court for the lack -- lack of sufficient basis?

A. I don't recall.

Q. Okay.

Is that you don't recall that ever happening or you know it hasn't happened or you're just not sure?

A. I don't recall it ever happening.

Q. Okay.

A. I don't understand the legal parameters of that question. Lack --

excluded for?

Q. Has -- has any court ever decided that the opinions you offered lacked sufficient basis and therefore could not be heard by a jury?

A. Not to my knowledge.

Q. Okay.

You would have wanted to know that, right?

A. Yeah, I think so.

Q. Okay.

Do you know someone named Martina Hufnal?

A. Martina who?

Q. Hufnal?

A. Doesn't ring a bell.

Q. Let's see. Sorry, so let's go back to Dr. Falconer for a second.

You testified before that without access to your email, you can't recall whether you -- when you reviewed his declaration it was a draft or it was signed, right?

A. Correct.

Q. Okay.

But if you look at your email, you would be able to determine that, right?

A. I'm not sure. We've changed email systems, and I may not be able to retrieve it, but I would certainly be able to try.

Q. Okay.

So you'd be able to do that search and you'd just search for Dr. Falconer's name or for counsel's name?

A. Yeah, I don't believe we exchanged -- if we exchanged personal emails, I don't believe we did, but if we did, I would be able to try and look at it in our email system.

Q. Okay. And maybe my question is a little bit different.

If you -- my question is about whether or not the version of Dr. Falconer's report that you reviewed was final or in draft form, and one possibility I suppose is that he sent it to you in one of those forms. Another possibility is that counsel sent it to you

in both -- in -- in one or both of those forms.

A. No, I -- may I answer?

Q. Please.

A. I think that is -- that I would be sure that it was counsel provided his -- his form -- his whatever document he sent me, but whether it's version final draft, signed, unsigned, I can't recall.

Q. You don't know if it was version 1.0, 2.0, 5.0, you just don't remember?

A. No.

Q. Okay.

But you would be able to determine that by looking through your email, right?

A. No. I would need to know what version I looked at at the time and how I looked at it. It might have been a share screen or something that I wouldn't necessarily by looking at the email know how I reviewed his document.

Q. Okay.

Do you recall whether you ever used a share screen to review

Dr. Falconer's report?

A. I don't recall.

Q. Okay.

But eventually, you were provided with the final copy of his declaration?

A. Correct.

Q. Okay.

And you may have been provided with earlier copies by email. Not sure, right?

A. Right. Draft copies.

And I certainly was aware of the themes that were being developed in Dr. Falconer's report.

Q. As conveyed to you by counsel, right?

A. Correct.

Q. Okay.

And so if you searched your email for, for instance, a Fish and Richardson email address, you would at least be able to find what versions of his report were in your inbox even if you couldn't eliminate that you'd also looked

at others?

MS. CHACON: Objection; asked and answered.

A. I think I've already answered the question.

Q. Well, I haven't asked the question before, so no.

Maybe I'm confused.

If you searched your inbox for a Fish and Richardson email address, that would turn up whatever versions of Dr. Falconer's report were emailed to you, right?

A. If they were emailed to me.

I don't know if I was provided with a paper copy, for example.

Q. All right. So if they were emailed to you.

A. If they were emailed to me.

Q. Did you ever meet with Fish and Richardson attorneys in person before signing your report?

A. No.

Q. Okay.

Did they ever mail hard copy

documents to you?
A. Yes.
Q. Okay.
When?
A. I don't recall.
Q. Do you recall if it was more than a week ago?
A. Yes.
Q. It was more than a week ago?
A. It was more than a week ago.
Q. How long ago was it?
A. In -- prior to the declaration signing. Prior -- in the process that went forward to create this declaration.
Q. Okay.
And you don't recall whether anyone ever mailed in hard copy form to you a version of Dr. Falconer's declaration?
A. I do not recall.
Q. Okay.
If -- if they had, would you still have that document?
A. Not necessarily.
Q. Okay.

But you personally verified the accuracy of the citations to Dr. Falconer's report in your report, right?

MS. CHACON: Objection; asked and answered.

A. If you're asking me did I read every one of the citations in Dr. Falconer's report, meaning read the references, the answer is clearly no.

If you're asking me if I read the report from the point of view of a -- of a person of ordinary skill in the art and a treating clinician, the answer is yes. I was aware of the major themes and so was able to perform a review based on prior information communicated through counsel.

Q. Okay. So maybe I can't tell if we're saying the same thing or something different.

You didn't -- there are numerous citations to Exhibit 1004 which is Dr. Falconer's declaration in your declaration.

A. Correct.
Q. Okay.
It's your testimony that you did not determine whether each of those citations was accurate, right?
A. You're asking me now if my declaration is accurate relating to Dr. Falconer's.
Q. Yes, that's right.
A. And the answer -- the answer is correct, yes.
Q. Okay.
So whenever you received his final report, you then plugged in the citations to his expert declaration into your declaration?
MS. CHACON: Objection; mischaracterizes testimony.
A. I -- I think --
MS. CHACON: Asked and answered.
A. Yeah, Dr. -- the themes were very clear. The direction of the important elements that were required both of my report and his report were known to each other through counsel, and the

creation of the final documents allowed a straightforward verification "no, this is important," "this should be cited," "this should be not."

As to the specifics of me reading each and every one of his references, the answer is no, I did not. But certainly in terms of I stand by my report, my declaration as being accurate with the exception noted.

Q. Okay. So, you said both your report and his report were known to each other through counsel.

You know what was told to you about Dr. Falconer's opinion.

Do you know what was told to Dr. Falconer about your opinions?

A. I presume he was -- he was well informed in the collaborative process that I've mentioned.

Q. You presume that, but you do not personally know that, right?

A. Well, I know that he -- well, he was meeting with counsel and -- and -- and developing the themes that I have alluded

to, and therefore, the clinical use of intravitreal agents would have been uppermost on his mind. I think it's -- I think it's clear that he was well informed as to the themes of my report.

Q. Okay.

And those are the themes developed by counsel, right?

MS. CHACON: Objection; argumentative.

A. Those are --

MS. CHACON: Asked and answered.

A. -- things that were developed by me, by -- developed by collaborative effort, developed by Dr. Falconer in this collaborative process.

Q. Okay.

Did you tell Dr. Falconer that the POSA would select an injection volume of 70 microliters?

A. That was clearly a -- a -- clearly a target that was communicated through our collaborative conversation by communication between counsel and Dr. Falconer.

Q. Okay.

So, yes, perhaps through counsel, but, yes, you told Dr. Falconer that the POSA would select an injection volume of 70 microliters?

MS. CHACON: Objection; misstates the witness's testimony and argumentative.

BY MS. KAYALI:

Q. You can answer.

MS. CHACON: Counsel, you've got a minute left. So I suggest if this is how you want to use your time, you wrap it up.

MS. KAYALI: I suggest you conform to the appropriate objections.

A. So, the question is did I point him exclusively to 0.70, the answer is no.

Did I point him to an injection volume as low as possible with a viscosity that could comfortably go through a 70 -- a 20-gauge -- excuse me, 30-gauge needle and would I ask for that to be proximate -- to be 8 milligrams, the answer is yes.

But did not exclusively discuss that. There were a range of things being considered because, just like I want as low an injection volume as possible, he wants as high a volume as possible in order to arrive at an acceptable viscosity.

Q. Okay.

So you left the optimization of those parameters to him?

A. No.

MS. CHACON: Objection; mischaracterizes.

A. I just described that I had very clear preferences of dose parameters that would have guided the conversation between the formulation chemist and me. So I didn't leave it to him. It was a collaborative process, as I have discussed.

Q. That consisted of a 30-minute conversation the day before your expert report was due?

MS. CHACON: Objection; asked and answered.

A. I've already answered that.

It was a collaborative process by a person of ordinary skill of the art as I have defined it in my report.

MS. CHACON: Can we get a check on the time, please?

THE VIDEOGRAPHER: Seven hours.

MS. KAYALI: Okay.

Well, I'm told, Dr. D'Amico, by your counsel, that I have no time for further questions. So with that, I will conclude my questioning.

Do you have any redirect?

MS. CHACON: I may have a little bit of redirect.

Give me about five, ten minutes.

MS. KAYALI: Sure.

MS. CHACON: And then we can go back on the record.

MS. KAYALI: Great.

MS. CHACON: Thank you.

THE VIDEOGRAPHER: The time now is 6:00 p.m., and we are off the record.

(Recess taken.)

THE VIDEOGRAPHER: The time right now is 6:15 p.m., and we're back on the record.

EXAMINATION BY

MS. CHACON:

Q. All right. Dr. D'Amico, I'm going to ask you a few questions, okay.

All right. So, earlier today you were asked about various legal standards that you applied in preparing your opinions in this case.

Do you recall that?

A. I do.

Q. Okay.

And we were looking at your report when you were asked those questions by counsel, correct?

A. Yes.

Q. So let's get out your report, it should be in front of you. And again, that's Exhibit 1003.

So, I'd like to have you take a look at your table of contents which starts on page -- look at page 3 of your report and in there there's a Section 9

"Legal Standards."

Do you recall looking at that?

A. I do.

Q. All right. And if you could go to page 68 for me, and we're going to take a look at paragraph 118.

Let me know when you're there.

A. I'm there.

Q. All right. So, in this paragraph, you state: Counsel for Alvotech has informed me that when assessing whether a claim is obvious, I should consider little Roman numeral (i) the scope and prior art; (ii) the level of ordinary skill in the art; (iii) the differences between the prior art and what is claimed; and (iv) any, quote, secondary evidence that may indicate that the claims are not obvious.

Do you see that?

A. Yes.

Q. Okay.

And do you recall counsel asking you about that earlier today?

A. I do.

Q. Okay.

Now, she first asked you about the scope and the content of the prior art.

Do you recall that?

A. Yes.

Q. And I believe as an example you pointed us to, and we're going to go back to your table of contents for a moment, so hold -- hold that page that you're at and then just flip forward to the table of contents for me, and I believe you pointed her to Section 10.

Do you recall that?

A. I do.

Q. Okay.

Are there other places in your report that you discuss the scope and content of the prior art?

A. Yes.

Q. And where is that?

A. The entirety of Section 10 and also in various segments related to the grounds of the report.

Q. Okay.

So let's talk about the -- the grounds for a moment. So we'll stick here and look at the -- in the table of contents in the next section, which is Section 11, do you see that?

A. Ground 1, yes.

Q. Okay.

And what do you understand Ground 1 to be?

A. Ground 1 is that the combination of Vitti, the Australian label and the Larson patent would have rendered the claim ob -- the claims obvious.

Q. Okay.

And if you flip through your table of contents, you similarly have sections regarding the other grounds that you opine on, correct?

A. Correct.

Q. All right. So, looking at Ground 1 and how this section is structured, what do you understand Section A to be conveying?

A. What do I -- that the combination of those three things would

give a reasonable chance of success to develop an 8 milligram formulation in a -- in an acceptable vitreous volume, injectable volume, probably of 70 microliters as the initial target with a viscosity of between 5 and 15 centipoise.

Q. Okay.

And just to short-circuit that, Doctor, at least to read Section A's subheading, it's discussing the, I guess, motivation and reasonable expectation of success?

MS. KAYALI: Objection; leading.

BY MS. CHACON:

Q. Correct?

A. That is correct.

Q. All right. So, we look at subheading B.

What is subhead -- what are you trying to convey in subheading B?

A. To break out the individual phrases of independent claim 1.

Q. Okay.

And so --

A. In order to render them obvious.

Q. So in looking, in forming your opinions, just to make sure I understand correctly, you are looking at each of the claims that's been in dispute, right?

A. Correct.

Q. And are you looking at each of those claims in comparison to the prior art?

A. Yes.

Q. Okay.

So, if we look back at paragraph 118 in your report, counsel also asked you if you considered the differences between the prior art and what is claimed.

Do you recall that?

A. Yes.

Q. And is that what you're trying to convey in section B and other sections of your report where you're evaluating the claims?

MS. KAYALI: Objection; leading.

A. Yes.

Q. All right. I would now like you -- do you recall, Dr. D'Amico, that we had extensive discussion today about the

Vitti prior art reference?

A. Yes.

Q. Okay.

And do you discuss Vitti throughout your report?

A. Yes.

Q. And during counsel's examination today, she pointed you to a couple of portions of your report.

Do you recall that?

A. Yes.

Q. Do you recall that she pointed you to limited portions of Vitti as well?

A. Yes.

Q. Okay. Let's take a look at Vitti. So if you could bring it back up, it's Exhibit 1007, for me.

All right. And do you recall, Dr. D'Amico, that counsel was asking you a host of questions about what, if anything, Vitti teaches you about dose?

A. Yes.

Q. All right. I'd like you to turn to paragraph 139 in Vitti.

Let me know when you're there.

A. I'm there.
Q. Okay.
Did you consider paragraph 139 in formulating your opinions regarding Vitti?
A. Yes.
Q. And what does Vitti teach a person of ordinary skill in the art about dose?
A. That a dose of aflibercept of 0.5 milligrams to about 10 milligrams of an anti-VEGF antagonist, exempli gratia aflibercept.
Q. And so did this paragraph inform your opinions at all of the teachings of Vitti as it relates to dose?
A. Yes.
Q. All right.
Doctor, and I want to ask you a couple of follow-up questions regarding counsel's inquiry on the Larson reference. So if you want to get that out, and that's Exhibit 1010.
All right. So hold that and then you're also going to go to your

report.

So, if you could please turn in your report to paragraphs -- let's do this. If you could go to -- all right. So, actually start for me on page 86 of your report. And I just want to orient to you what section this is.

Let me know when you're there.

A. This -- this page has two numbers, it's 84 and 86. I presume you're using bottom numbers. It says Vitti.

Q. Yes, the bot -- the bottom number in your report that's page 86 --

A. I'm there.

Q. Okay.

And is there a heading A on the page that you're looking at?

A. Is there a heading A on the page?

There's number 9 I'm looking at here.

Q. I'm sorry, you're on page 86?

A. Sorry, page -- double page numbers.

Yes, there's a heading page --

on page 86 there's a heading A.

Q. Okay.

And what do you understand this section to generally be discussing?

A. Again, the combination of the teachings contained in Vitti, the Australian label, and Larson would have provided a person of reasonable skill in the art with a reasonable expectation of success in the matter at hand formulating a high dose aflibercept.

Q. Okay.

So we're going to stay in this section, and I would like for you to go forward to paragraph 183 in your report.

A. I'm there.

Q. Okay. Go ahead and take a read through page 180 -- I'm sorry, paragraph 183.

A. (Witness reads document.)

Q. And then while you're doing that, please also take a look at paragraph 184, and let me know when you're ready.

A. (Witness reads document.)

I have completed my reading of

those two paragraphs.

Q. Okay.

And based on these paragraphs that you include in your report, what, if anything, do you conclude that a POSA would have understood from Larson regarding VEGF antagonist formulations?

A. That viscosity of specifically mentioned ranibizumab and aflibercept, I believe -- let me make sure that aflibercept is mentioned in here.

That the injection of viscosity would be less than about 20 centipoise or more peripherally particularly around 10 measured at 25 degrees C.

Q. And is this based on your reading of Larson?

A. Yes.

Q. And you stand by your opinions in your report regarding Larson?

A. I do.

MS. CHACON: All right.

Dr. D'Amico, I have no further questions for you at this time subject to any redirect from counsel.

FURTHER EXAMINATION BY
MS. KAYALI:
Q. Dr. D'Amico, at all times that I was asking you questions, did you have your report available to you?
A. I did.
Q. Okay.
And do you stand by your testimony in response to the questions I asked you today?
A. I do.
Q. Okay.
And nothing you just said in response to the questions from Alvotech's counsel is intended to, like, recant or modify what you testified to under oath in response to my questions, right?
MS. CHACON: Objection; vague.
A. It -- a clarification, but define modify.
I mean, clarification was provided. Additional -- for example, I had -- as I recall, we could have it read back, that I said that I didn't -- I wasn't clear whether there was dosage

information in Vitti, and I said that I didn't know, and we came to the point that there probably wasn't, but with redirect, there's a clear phrase in Vitti that expresses dosage.

So that's an example of a modification that is a correction, yes.

Q. Okay.

But you stand by the testimony you provided to me under oath today, correct?

A. Yes.

Q. Okay.

And in the time since -- before answering questions from Alvotech's counsel, did you speak to Alvotech's counsel?

A. No, not -- nothing related to the case.

Q. Okay.

And so you didn't -- you weren't asked those questions and you didn't provide answers?

A. Not at all.

Q. Okay.

So you stand by your testimony under oath?

A. Yes.

MS. KAYALI: Okay.

I think with that you're a free man.

MS. CHACON: Thank you, Dr. D'Amico.

THE WITNESS: Thank you.

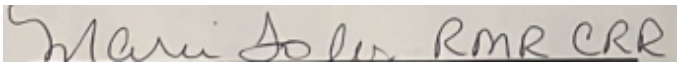
THE VIDEOGRAPHER: The time right now is 6:26 p.m., and we're off the record.

(Deposition adjourned at approximately 6:26 p.m. EST)

I, MARIE FOLEY, Registered Merit Reporter, Certified Realtime Reporter, and Notary Public for the State of New York, do hereby certify that prior to the commencement of the examination, DONALD J. D'AMICO, M.D., was duly sworn by me to testify to the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a verbatim transcript of the testimony as taken stenographically by me at the time, place and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not financially interested in the action.



COURT REPORTER
Registered Merit Reporter
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Dated: June 5, 2026

Case: Alvotech v. Regeneron
Witness Name: Donald J. D'Amico, M.D.
Deposition Date: 06/02/26

Please be advised that the transcript in the above referenced matter is now complete and ready for signature. The deponent may come to this office to sign the transcript, a copy may be purchased for the witness to review and sign, or the deponent and/or counsel may waive the option of signing. Please advise us of the option selected. Please forward the errata sheet and the original signed signature page to counsel noticing the deposition, noting the applicable time period allowed for such by the governing Rules of Procedure. If you have any questions, please do not hesitate to call our office at (202)-232-0646.

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Witness Name: Donald J. D'Amico, M.D.
Deposition Date: 06/02/26
I do hereby acknowledge that I have read and examined the foregoing pages of the transcript of my deposition and that:
(Check appropriate box):
( ) The same is a true, correct and complete transcription of the answers given by me to the questions therein recorded.
( ) Except for the changes noted in the attached Errata Sheet, the same is a true, correct and complete transcription of the answers given by me to the questions therein recorded.

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Errata Sheet

NAME OF CASE: Alvotech v. Regeneron

DATE OF DEPOSITION: 06/02/26

NAME OF WITNESS: Donald J. D'Amico, M.D.

Reason Codes: 1. To clarify the record.
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3. To correct transcription errors.

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From _____ to _____

Page _____ Line _____ Reason _____
From _____ to _____

Page _____ Line _____ Reason _____
From _____ to _____

Page _____ Line _____ Reason _____
From _____ to _____

_____
DONALD J. D'AMICO, M.D.

A
A's 451:9
a.m 1:19 2:7 9:2 9:10 124:7,11
Abicibar 164:13
Abicipar 164:14 164:15 165:14 165:14
Abicipar's 165:9
ability 16:16 111:10 187:10 414:20 461:13
able 19:15,22 41:4 76:8 152:18 161:13 165:15 173:15 174:7,19 177:21 215:11 295:3,6,19 302:14 348:16 348:17 364:12 364:18 421:6 421:11 435:2,5 435:6,9,15 436:14 437:23 440:16
abnormal 72:3 230:23
abnormalities 136:23
abroad 47:9,16
absence 109:9 144:15 252:10
absent 462:21
absolute 418:24
absorption 83:7 83:18
abstract 424:10 425:1
absurd 206:17
abundant 239:13
academic 71:19
accept 309:11
acceptable 299:16 312:6 335:18,22 352:10 365:25 367:16 427:13 445:6 451:3
accepted 171:2
access 47:6,13 52:4,23 53:7 53:11,16 201:16,21 202:3 204:24 293:8 409:16 434:20
accidental 132:17
accidentally 132:1,2,7 183:25 375:24 389:20 408:24
accompanying 152:15
account 138:21 237:4,15 431:25
accumulate 112:9,14 123:16
accumulated 241:10
accumulates 115:17
accumulating 115:15
accumulation 112:8,11
accuracy 440:2
accurate 48:21 62:17 389:17 398:7 441:5,7 442:9
accurately 50:13
acetone-like 296:13
achievable 221:22 222:1 297:24
achieve 163:17 193:19 332:7 365:24 377:9
achieved 274:6
achieving 262:14 274:7
acknowledge 463:10
act 380:2
acting 72:11
action 254:17,23 262:11,15 263:8 268:4 274:23 278:17 280:13 282:6 284:4,7 376:13 377:10,13 378:12 380:3 387:12,25 388:9,14 461:16,19
active 47:13 427:17
activities 70:3
acts 227:1
actual 56:4
acuity 169:23 384:7
acute 92:14 94:1 94:4 98:10 99:11 123:12
add 54:16 55:23 56:2 425:22
added 55:18 335:23
addition 166:12 166:13
additional 139:8 149:7 167:21 217:21 279:20 282:15 320:2 321:21 405:12 405:13 410:11 458:22
additions 54:19
address 63:17 211:24 212:22 212:25 437:22 438:10
adequately 398:8
adjourned 460:13
adjust 192:25 427:23
adjusted 193:2
adjusting 192:16 420:9 420:10
adjustments 427:12
adjuvant 72:5
administer 78:6 133:2 134:11 140:16 144:5 152:19 296:3 369:17,25 370:25 373:16 373:24 377:8
administered 72:5 74:11 108:12 128:5,7 128:13 131:9 132:3,8 134:24 135:8 138:25 161:20 168:20 219:20 224:12 248:14 259:25 282:14 285:24 321:12 405:25 408:8,25 409:5 409:18 424:15 429:4,5,24
administering 72:24 129:25 135:24 137:12 140:14 153:10 420:20,23
administration 71:15 78:3 109:7 117:25 119:18 131:17 134:20 236:14 248:23 358:8 358:11 365:25 393:19 424:23 427:19 428:5 428:19
admitted 351:20
adult 75:6
advance 146:14 146:15,19,20 146:23
advantage 189:3 395:17
adverse 91:17 91:18 93:9 132:19 175:17
advice 303:1,4
advise 462:11
advised 462:6
affect 80:13 88:19 89:4,10 148:22 418:8
affinity-enhan... 243:20
affinity-matur... 243:20
affirm 10:17
aflibercept 36:6 38:4 39:4 162:3 187:3 195:11 196:16 196:18 219:15 221:23 224:6 224:17 226:18 226:19,20 227:1 228:25 229:8,14 230:12,18 234:2,4,8,17 235:2,15,19 255:10,15 256:6 259:11 260:5 263:6 266:9 268:3,6 268:7,20,21,24 269:4,5 270:21 272:25 274:13

278:16 280:12 281:2 282:5 283:25 284:3,7 285:15,24 286:10 296:2 301:20 307:17 309:17 310:23 311:3 312:8 314:13,19,20 316:14 323:19 324:16 326:15 327:9 328:9 337:11 338:4,6 338:21 339:12 339:15,20 340:5,8,12,24 340:25 341:3,6 341:7,24 342:10,24 343:5,9,20 345:2,12,15,21 345:23 346:10 346:20 347:3,8 347:13,16,20 347:20,22 348:7,8,15,20 348:24 349:20 350:24 351:25 352:2,25 358:20 359:21 360:2,21 363:15 367:13 368:16 369:17 370:7,16 371:1 371:13,18,21 372:20 373:9 374:5 375:2 376:12,21 377:8 378:11 378:20,22,23 379:5,8,10,18 379:19,22 380:12,16 387:11 388:8 388:25 393:15 399:14 400:20 400:24 404:13 413:21 414:2,5 414:22 415:1,6 415:20 416:2,7 416:22 417:5 418:7,11 427:6 432:11 454:10 454:13 456:11 457:9,11

afraid 188:19 223:6 228:21 316:24

African 104:6

aftermarket 175:16

AFTERNOON 5:10

afterward 152:20

age-related 20:1 165:23 249:22

aged 69:23

agencies 411:1

agent 78:3 91:11 97:25 116:20 139:15 146:14 156:3 159:18 160:19 165:1,4 166:6 167:12 167:15 176:16 178:4 185:24 186:18,23 187:13 190:9 239:4,15 254:16 256:15 257:12 258:3,5 258:21,22,24 267:19 426:22

agents 37:9 76:25 78:19 92:4,6,14 93:4 97:3,13 99:12 107:21 117:15 135:15 144:25 149:15,18 150:2,17,20 153:10 162:2 164:5 167:7 168:21,22 169:14 177:15 178:17 179:19 180:4 185:9 187:5,16 188:22 189:12 189:19,25 238:3 242:1 254:3 255:7 256:25 257:1 259:25 262:10 295:10,14 358:8,16,22 427:13 431:13 443:2

aggregate 184:13

aggregates 180:11,22 181:3,9,16 182:20,22 185:5

aggregation 179:22,25 180:4

ago 18:18,24 70:8 80:4 150:5 217:16 391:6 439:7,9 439:10,11

agree 94:19 118:20 121:12 127:18 140:19 143:21 241:25 268:25 272:3 299:12 318:16 392:9,21 393:8 429:11,14

agreed 119:21 122:4

ahead 46:9 90:18 117:13 121:23 130:15 133:12 146:3 149:24 150:18 256:23 275:10 303:13 304:22 323:1 400:13 403:17 418:15 456:17

aiming 300:16 300:18 309:10 316:13

air 252:25

Al 12:25

Alcon 12:17 18:6 433:1

aliquot 253:12

alive 93:15,17 93:19,21 94:11

allay 152:9

Allen 245:2,16 245:16 246:4,7 246:19,21

Allergan 164:21

Allergies 149:10

allow 46:4 75:24 296:9

allowed 442:1 462:14

allows 88:9

alluded 442:25

alteration 107:7

altered 96:19 106:2

altering 98:1,8

Alvotech 1:4,4 7:7 9:13 10:9 17:4,8,11,16 32:17 210:22 247:9 304:24 448:11 462:1 463:7 464:2

Alvotech's 458:14 459:15 459:16

AMD 37:12 77:16,17 145:12,13 151:15,22,23 151:25 160:16 232:17

America 42:13 253:5

American 6:5,9 79:12 95:23

amino 80:12

aminoglycoside 80:16,24 82:16 83:9,11 84:3 85:4 107:5 108:8 109:8,22 119:19

amount 177:21 183:7 229:9 233:19 234:11

analysis 34:1 213:10 282:18 305:10 361:11

analytical 423:7

analyzed 141:15

analyzing 178:19

anatomic 103:22 110:13 116:2 120:10 123:12 392:4

anatomical 111:3,14

anatomy 86:13 103:12

anchoring 145:9

and/or 462:10

Andrew 3:17 9:22

ANG2 342:13 346:9 348:25

angiogenic 49:24 197:18 197:23 233:1

angiopoietin 342:6

animal 85:13 86:3,18,21 87:1 91:4 111:10 174:2

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 466 of 524

375:13,13
animals 91:5 98:10 175:12 417:6
answer 8:3 14:20 15:11 28:1 29:22 30:2 37:3 44:12 47:14 53:6 58:16,20 72:2 73:19 78:18 90:18 94:5 102:7 121:1 122:1 144:16 159:1 172:5,16 206:9 207:4 248:6 249:14 262:25 271:23 275:3 289:17,20,24 290:23,24 303:1 310:3 313:22 329:11 372:22 427:9 436:3 440:10 440:14 441:10 441:10 442:7 444:10,18,25
answered 26:21 26:23 27:12 39:11 43:19 44:10,11 45:12 45:20 46:21 118:19 119:12 121:17 122:16 123:8 140:23 166:9 202:14 206:8 259:1,2 260:14 262:18 262:22 263:20 291:10 292:24 333:9,10 366:12 390:19 438:3,4 440:6 441:20 443:12 445:25 446:1
answering 21:18 417:24 459:15
answers 14:11 317:17 459:23 463:15,20
antagonist 305:25 306:3 336:2,5,17 337:10 338:4 338:21 339:4,8 339:20,24 340:16,23,25 341:2 342:17 343:21,24 344:3,6,16,25 345:10,20,21 346:2 347:1,2 347:10,12 348:6 349:17 349:19 350:22 350:24 352:1 352:16 353:5 354:2,10 356:16,18 357:16 358:2 360:13 364:11 364:18 366:7 454:12 457:7
antagonists 342:22 344:22 345:11 347:21 348:14 357:6 359:8,9 431:2
anterior 98:18 98:23
anti 185:16 341:23
anti-ANG2 358:19
anti-angiopoie... 341:22
anti-inflamma... 72:10
anti-VEGF 37:9 76:25 78:19 149:15,18,22 150:2,16,20,23 152:1 156:2 159:18 160:18 164:5 165:1,4 166:6 167:7 168:21,22 169:14 171:9 180:4 185:9,24 190:7,9 197:21 197:22,25 238:3 239:3 242:1,14 249:17 254:3 254:16 256:15 258:3,5,24 259:25 260:19 262:9,16 266:5 342:6 358:20 383:7 384:14 385:24 394:5 394:15 396:10 426:22 454:12
anti-VEGFs 261:23
antibiosis 131:13 135:25
antibiotic 107:4 115:6 118:4 123:15 125:25 126:4 133:4 136:9,17 137:7 138:25 140:9 143:25
antibiotics 72:7 72:20 73:4 74:11,17 80:13 80:17,19,24 82:16 84:3 85:4 96:12 118:12 127:6 128:8,14,18,23 129:4,6,12,21 130:5,17,23,24 131:9
antibodies 185:8 185:11,18,23 186:12 198:7 203:4
antibody 243:18 244:13 250:15 250:16,17
anticipated 210:11
antidrug 185:8 185:11,18 186:12
anymore 69:14
Aphakia 97:8
aphakic 103:17 113:22 114:17
apologies 233:24
apologize 125:9 209:22 219:1
apparent 275:7 279:2
apparently 59:15 291:13
APPEAL 1:2
appear 187:6
appearance 10:4 120:11,12
APPEARAN... 3:1 5:4
appeared 99:16 110:12 255:25
applicable 462:14
applied 41:20 107:6 211:9 257:12 406:5 447:10
applies 82:8
apply 41:20 214:25 215:11 345:22 346:2 418:9
applying 307:4
appreciate 366:15
approaches 77:22
appropriate 116:6,7 127:5 127:13,22 137:7 177:17 177:21 194:6 200:3 286:7,17 295:23 296:7 312:11 317:11 328:15 417:14 444:16 463:13
approval 139:18 186:23 187:11 236:20 253:8 264:24 381:13
approvals 186:22
approved 139:14 153:13 165:21 167:2 236:13,19 239:11 240:2,6 250:5 252:2,4 252:7,16 256:16 260:18 267:17 404:8 416:4
approximately 11:17 100:25 101:1 103:1,19 301:9 363:1,10 363:20 367:15 460:14
approximation 102:24 234:19
apt 105:12
aptamer 238:23 238:24 266:5 267:16,16
aqueous 96:25 97:22 98:20
arabesque 75:19
arbitrary 158:16
Archive 6:14 106:19
area 89:10 181:17,19 232:19 429:8

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 467 of 524

areas 155:23
arguable 283:20
argue 14:18 266:18
argumentative 376:5 443:10 444:8
arose 203:22
array 154:16 218:8
arrive 225:2 318:20 329:1 445:6
arrived 428:24
art 19:22 34:5 35:4,7,13 36:21 57:12,19 57:25 58:5 67:22 68:2 76:1 143:15 196:24 197:13 198:10,14 199:9,15,21 200:8,14,17,23 201:7,23 202:6 202:13,19 203:8,14 204:6 204:10,20 205:8,23 210:3 210:9,10,17 211:1,2,3,23 211:25 212:8 212:14,17,20 213:11 214:1 214:25 216:19 222:6 223:21 262:8,9 263:13 285:7,15 288:4 299:18 303:24 324:11 328:8 331:4 337:22 339:16 340:7 342:4 343:7 344:23 345:1 345:17 346:18 347:14 348:19 358:25 359:5 364:5 366:22 368:23 381:6 383:13 386:13 395:13,14 404:11 405:11 440:13 446:3 448:14,15,16 449:4,19 452:8 452:14 453:1 454:8 456:9
artery 191:6
article 6:5,9,13 6:18 79:12 89:12 95:23 106:19 124:24 128:2 158:13 184:24 386:11
articles 71:16,17 74:13 129:8 154:7 159:3,9 159:14
Asian 104:6
aside 50:15,18 73:25 144:2 250:8 411:18
asked 14:15 26:20 27:11 32:9,23 33:23 39:10 44:9 45:11 64:24 92:20 118:18 119:11 121:16 122:16 123:7 129:16 140:22 144:18 166:8 206:7 248:24 258:25 260:13 262:17 263:19 284:13 292:23 327:7 333:8 366:11 376:10 387:9 390:18 395:25 438:2,6 440:5 441:20 443:12 445:24 447:9,16 449:2 452:12 458:10 459:22
asking 19:7 45:18 46:19 59:8 120:5,5 140:12 149:25 150:7,16 155:14 158:19 160:2 168:25 169:7 174:17 190:5 194:18 196:13 202:9 202:21,22 206:2,4 208:19 213:8 220:7 249:14 258:16 259:17 262:7 271:22 285:2 287:23 305:20 305:21 313:10 313:11,13 316:22 322:11 322:12,13 329:23 338:9 343:16 357:10 369:22 382:11 387:2,4 410:5 415:8 416:14 423:25 440:7 440:11 441:6 448:23 453:19 458:4
asks 418:23
aspects 341:22 369:4 386:25
assent 94:21
asserting 61:3
assertion 342:8 398:4
asserts 126:22
assess 404:22
assessed 405:1
assessing 210:23 448:12
assessment 157:3 372:4
assigned 143:7
associate 9:25
associated 149:10 405:13
association 131:10
assume 15:11 24:5 35:6 140:7 151:24 175:21 195:25 204:4 209:2 322:22 347:14 410:20 411:3 427:11
assuming 161:3 161:4 213:4 409:15
assumption 81:21 321:11 363:14
assumptions 213:7
assurance 123:1
astray 128:20
attached 463:18
attempt 169:21
attempting 169:24
attempts 265:23
attention 155:21
attest 209:5,6
attesting 43:9 204:18
attorney 14:15 14:21 17:24 289:18 461:15 461:18
attorney/client 29:22
attorneys 18:2 22:12 438:21
attracted 225:4
attracts 229:2
attribute 157:23
AU 218:23 219:5 219:11 332:25 430:19
audible 14:11
August 6:7 79:13
Australia 297:2
Australian 219:18 224:11 294:2,11 311:9 311:25 320:25 323:12 324:1 324:17,23 325:1,23 327:10,17 328:6,7 332:10 332:25 333:17 335:7 354:15 362:11 365:3 367:10 374:12 398:25 399:11 410:22,22 411:2,6,11,14 450:11 456:7
authentication 38:8
author's 272:16 398:9
authored 289:4
authorities 410:12
authority 41:25 157:23
authors 80:11 114:14 138:18 141:11 266:12 391:17,21 394:24 396:17 397:8 398:11 398:12
avail 56:8
available 16:3 17:4 36:20 56:8 58:23 127:17 133:21 136:16 144:24 155:22 159:14

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 468 of 524

166:17 176:17 187:15 188:1 188:17,22 189:6 221:10 221:11 223:20 223:23 224:9 246:19 280:5 280:10 299:20 299:21 365:2 403:19 404:12 405:22 427:1 458:5
Avastin 162:4 186:25 188:5 243:22 250:14
Avenue 3:19
average 103:17 273:20 279:23 392:4
avoid 132:13 135:24 294:25 295:1
avoiding 135:10
awake 44:2,7,14 44:19,22
aware 30:8,12 45:22 48:14 52:18,22 54:18 128:1 164:6 177:10 184:18 184:19,21,23 185:7,10 186:2 205:25 213:21 213:24 214:3,6 214:9 233:14 233:17 240:23 242:21 251:25 254:4 344:21 385:12 396:2,4 414:24 415:4 415:17,25 416:12,15,17 417:3,4,12,15 417:18 426:21 428:1,6 437:13 440:15

B

B 6:2 7:2 83:11 227:16,21,22 451:18,20 452:18
baby-sitting 191:7
back 51:20 65:25 95:15 119:15 124:12 124:13 144:3 144:21 150:4 151:10 153:12 153:18 157:13 166:15 167:24 196:8 198:19 203:17 211:20 218:16 226:13 231:10 233:4,4 233:25,25 286:11 289:3 303:25 306:20 308:2 310:6,10 313:17 324:8 357:21 361:7 371:6 381:7 386:3 387:6 398:21 412:9 431:16 434:18 446:19 447:2 449:8 452:11 453:16 458:24
background 49:22 63:16 175:10 199:10 200:9 202:20 204:21 205:9
bacteria 126:14 257:6
bacterially 184:6
bad 89:3 148:19 268:14 294:24 295:1
barely 177:25
bargain 136:6
Bascom 67:3 252:21
base 115:5 363:14 369:4
based 81:25 91:10 108:5 110:13 115:11 137:20 140:12 161:16 162:14 174:8 180:9 187:25 221:9 307:18 321:11 323:8,11 324:16 327:9 327:14,16 440:16 457:3 457:16
baseline 156:15 280:1
basic 178:5 307:16
basically 188:3
basing 354:15
basis 82:21 85:17 89:9 91:11 105:9 114:13 127:18 132:25 134:9 161:9 169:3 220:3 221:15 252:1 319:6 323:4,14 349:25 350:4 399:18 414:11 433:15 434:4
Bates 7:7 247:9
baths 357:2
bear 36:22
bed 45:1,4,10,19 46:12
bedtime 115:8
began 35:1 261:11 419:13
beginning 82:12 97:19 113:14 161:2 260:17 261:22 337:19 391:14
begins 305:10 359:14
behalf 3:3,14 9:19 10:8
behave 83:10
belief 42:17
believe 13:8,11 21:5 51:18 60:21 75:4 103:1 107:15 126:9 168:5,21 175:8 227:17 234:6,16 240:15 245:2 246:8,9 250:21 251:14 252:23 253:6 254:5,15 262:12 269:20 270:23 275:15 280:14 287:18 290:14 291:10 291:12 302:4 302:16 303:14 303:23 309:10 314:5 338:8 357:18,22 385:17 426:5 432:20 433:6 435:12,14 449:7,12 457:10
believed 42:18
bell 434:16
belong 216:13
Belted 102:25
benefits 151:20
Beovu 188:9,12 188:24,25
best 14:25 15:9 16:16 18:19 19:14 41:1 152:9 153:14 153:22 154:1,4 154:6 268:2,9 268:12,12,14 285:3,4 350:15 432:24 461:13
bet 265:6
Betadine 152:23
better 40:20 44:24 48:12 60:9 68:8 83:24 89:16 94:5 112:21 122:23 127:23 158:18 160:11 163:22 166:16 170:9 178:13 183:14 185:17 196:17 253:25 259:18,18 265:1 266:22 284:4,13,14 309:15,16 312:4 360:10 376:1 377:9 395:22 397:15
bevacizumab 243:22 250:12 250:13,19 251:9,17,19,22 252:4,7 253:24 254:6,8,10,22 255:2,14,21 256:2,4,10 260:6 267:5,7 267:10,22,24 432:11
beyond 32:13 73:24 133:21 240:22 279:5 409:25
big 250:25 251:1 251:2 326:18
bigger 97:1 111:9 158:7 190:2 421:13
bin 158:20
bind 234:4 239:19 244:10

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 469 of 524

251:22
binding 229:3 229:10,13 230:17 234:8 234:10 244:13
binds 228:14 229:2,5 230:12 234:17 244:15
bio 70:15 123:25
bioavailability 83:7,19
biological 147:11
bit 177:22 265:5 298:8 435:18 446:15
biweekly 162:22
bizarre 75:18
bizarro 75:19
black-and-white 166:23
blanket 136:25
bleeding 72:6
blind 133:18 163:5
block 278:20,21
blood 231:23,24
blue 426:17,17 426:17,17
board 1:2 46:2 75:8 374:23 375:25 378:18 379:2 389:21 397:8,19
body 36:20 37:8 112:14 115:10 115:16 149:3 159:12 180:15 184:24 185:19 228:17 232:2,6 232:10 233:12 328:25
body's 97:19
bolded 87:10 106:8
bomb 135:21
Boo 107:2
bore 421:10
borne 171:13
bot 455:12
bottom 15:10 31:13 40:23 209:21 339:1 383:2 389:12 455:11,12
bound 228:10
box 463:13
brackets 330:23
branch 36:18
branches 66:18
bread 166:17
break 123:25 124:1,3,17 172:18 200:1 207:21 226:2 281:15 347:24 411:20 451:21
breakdown 232:20
breaks 180:16 306:24
Bressler 4:4 10:4 16:6,9,12 77:9 77:12,16
Bressler's 76:5
brilliant 426:17
bring 167:14 261:10 328:24 453:16
broad 116:14 134:24 330:16 330:20 331:7 333:15,20 362:7,15
broader 78:24 223:11 361:17
broadly 175:7
broken 178:23
brolucizumab 432:11
brought 36:22 72:8 144:20
buckets 161:17
build 319:24 332:17
Building 223:14
bunch 143:14 253:12
bungle 15:4
burden 163:1,2 163:16,21 165:5 168:24 224:7 261:7,14
buried 374:15 377:23
buy 253:9

C

C 227:16,21,22 457:15
calculate 301:6 307:16 309:20 333:21
calculated 113:19 114:14 340:5 364:7 367:14
calculates 313:23
calculation 115:15 299:17 312:19 314:6 321:25 323:9 323:11 324:2,3 327:21 328:12 363:19
calculations 115:20 317:2,6 317:18 318:3 319:5,10 332:15 354:21 365:18
calculator 309:21,24 310:14
calendar 47:6,13 52:5,24 53:8 293:8
California 3:8
call 31:17 46:2 73:13 155:19 162:25 230:3,8 462:16
called 12:16 17:15 80:20 87:25 152:25 164:13 227:23 231:1
calling 166:20
calls 20:8,18 35:14 36:10 39:11 94:16 104:15 114:25 116:11 117:2 119:12 120:22 120:23 121:17 121:22 122:14 122:15 123:8,9 126:21 133:6,7 133:11 134:14 137:16 138:10 139:11 140:23 147:19 159:6 159:23 165:10 169:16 170:7 170:16 171:25 173:21 180:24 182:2 190:4 193:14 199:18 209:13 236:6 242:5 259:12 260:14 262:21 325:15 337:16 346:4 373:20 403:15 417:1
camera 111:6
Camino 3:6
cancer 148:3 250:16 253:10
candidate 186:24
candidates 136:24
cans 102:3
capacity 157:11
capillaries 231:25
captures 231:7
care 14:1 78:2 163:23 420:14 423:19
career 135:10 417:8
careful 114:11 317:20
carefully 157:5
carriers 186:21
cascade 174:10
case 1:10 12:6 12:16,22,23 13:1,9,13 17:2 17:17 18:6,6 27:23 31:5 32:10 37:8 63:12 66:16 67:25 116:1 135:15 136:5 140:3 175:21 185:21 190:13 194:6 204:7,10 210:17 241:17 254:14 256:17 258:19 263:3 266:5 287:9,14 294:17 307:4 322:21 326:10 328:2 377:4 382:14 423:14 432:21,22 433:1,2 447:11 459:19 462:1 463:7 464:2
cases 11:19,20 12:9 113:23 114:18 136:3 184:19,22 191:9 224:13 325:2 326:8 374:13 389:22 399:22,24 400:5 401:3

402:9,24 406:6 410:16 433:3
Caspers-Velu 80:9
cast 11:11
cataract 70:16 72:16,21 73:4 73:7,10,13,16 74:1,5,12,17 97:9 98:6 103:18 108:13 126:19 127:3,6 127:24 128:8,9 128:12,14,19 128:24 129:2 129:12,16,22 130:6,8,11,17 131:5,8,10 133:4 135:1 139:15,20
categories 216:14
category 78:24 112:19 134:22 255:7
cause 92:17 108:16 120:6 132:19 186:6 191:5 232:22 253:12 320:8
caused 94:12 111:23 165:20 166:14
causes 16:21 92:3
causing 184:21
caution 58:17 289:16
cavity 99:19 103:3
cefuroxime 125:19,21,24 126:18 127:9 127:13,18,23 131:18 134:12 137:12 139:6 141:24 153:19
ceiling 386:15
cell 93:8 94:10 94:11 120:15 122:22
cells 88:15 89:18 89:25 90:7 91:20 93:5,6 94:13
Center 65:7
centipoise 38:17 219:25 220:17 220:24 222:4 224:21 293:20 296:17 324:4 451:6 457:13
central 33:10 36:18 191:6
cephalosporin 126:10
cephalosporins 126:9
certain 56:20 80:21 92:14 115:4,9,12 117:15 148:11 148:13 162:1 177:15 187:14 187:15,15 209:3 238:25 257:3 324:2 336:12 337:18 340:13 345:5 346:16 369:4 402:1
certainly 13:15 19:12 25:6 116:13 122:23 131:12 136:20 138:21 147:9 150:25 156:24 167:19 189:4 209:9 227:21 242:14 256:5 266:21 270:16 294:9 297:19 299:8 330:23 351:14,15 361:5 381:20 388:20 397:13 405:21,21 431:12 432:25 433:5,8 435:6 437:13 442:8
Certified 2:10 461:2,23
certify 461:4,9 461:14
cetera 21:7 35:25 59:3 75:25 81:19 86:14 115:10 115:10 122:23 127:1 138:1,18 143:13 184:23 187:16 234:15 266:10 282:13 286:25 287:3 289:5 295:7,7 295:22 317:13 317:17 342:1 346:17 409:22 410:12,19 413:4 418:20
Chacon 3:5 5:8 10:7,7 17:23 23:10,11 26:20 27:11 28:19,23 29:20 30:25 35:14 36:8 37:22 39:10 44:9 45:11,16 46:3 51:23 55:10 56:14 58:15 59:25 79:19 81:11 82:7 84:14 86:5,24 90:10 90:12,14 91:2 94:16 95:2 101:9 104:14 108:2 110:9 114:25 116:10 117:1,7,9,22 118:18 119:11 119:24 120:3 120:22 121:16 121:20 122:14 123:7,23 126:20 127:15 131:20 132:21 133:6,9 134:14 134:17 136:12 137:16 138:9 139:9,11 140:17,22 142:3 143:3 144:8 145:15 147:18 148:8 150:21 158:14 159:6,23 161:23 163:18 165:10 166:8 168:4,13,15 169:16 170:7 170:16 171:25 172:24 173:17 173:19,21 174:23 180:5 180:24 181:18 182:2,11,14 184:2 189:18 190:3 193:13 195:12 196:21 199:18 201:2 201:24 202:7 205:13 206:7 207:6,17 209:13 222:10 236:6 237:25 242:5 247:14 247:18 256:18 256:20 258:6 258:25 259:12 260:13 262:17 262:20 263:19 268:8 282:8,24 285:20 289:15 290:24 292:23 301:17 302:1 303:11 304:5 304:20 306:14 314:23 316:21 322:25 323:21 324:18 325:15 326:7 329:13 331:14 332:3 333:7 335:5,19 337:16 342:25 344:9 346:4 348:9 358:5 360:22 366:11 367:6 368:24 372:8 373:19 375:4 376:3 386:5 389:23 390:18 400:11 403:10,15 414:3 415:3,21 416:24 417:1 418:13,15 424:25 431:10 438:2 440:5 441:17,20 443:9,12 444:6 444:11 445:12 445:24 446:5 446:14,18,21 447:5 451:14 457:22 458:18 460:7
chacon@fr.com 3:10
chain 297:4
chair 154:9 206:18
chairmanship 68:22
chamber 98:18 98:18,24
chance 19:23 188:23 191:4 191:15 285:8 367:20 451:1

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 471 of 524

change 70:6 97:2,13 98:2,9 103:5 107:14 134:8 142:10 143:16,24 192:14,19 215:6 237:11 389:7
changed 69:9 96:20 192:21 435:4
changes 89:7 90:20 91:12,17 92:18,21 110:13 463:17
character 367:9
characteristics 156:15 180:10 254:11
characterization 142:7 156:23 165:25 198:5 203:2 400:17
characterize 112:18
characterized 369:2
characters 11:11
chart 431:16,18
charted 430:24
check 19:4 51:20 253:2 317:17 317:23 446:5 463:13
chemical 194:25 422:22 427:3,7 427:10
chemist 224:24 319:23 322:2 328:19 332:13 334:10 356:3 364:1 365:6 366:13,14,15 367:23 423:7 445:17
chemistry 58:9 64:1,2
chemists 426:4
Chicago 18:11 18:13 65:8 433:2
chief 232:3
children 111:11
choice 187:2,8 361:25 362:18
choosing 176:5 303:7
chopped 22:19
Chorong 3:18 9:22
chosen 108:11
chronic 136:22
circling 167:24
circumstance 118:5
circumstances 187:10 284:16
citation 390:8
citations 54:13 55:16,24 56:2 56:4 62:16 440:2,8,23 441:5,15
cite 244:22 245:23 250:21 251:5,13 275:20 353:12 377:20 381:17 381:18,20 382:14 383:14 384:16 385:21 390:15 393:21 394:1
cited 24:9 245:22,23 257:2 416:13 417:12,16 442:3
cites 352:20
citing 272:8 308:12 384:17
claim 35:12 210:11,18,24 214:25 220:4 223:11 323:15 448:12 450:13 451:22
claimed 211:3 212:15,21 213:12 214:2 215:19 303:9 448:17 452:14
claims 32:5,24 32:25 33:4,10 33:14,24 34:2 34:22,24 35:2 35:11,19 36:1 36:3,12,23,24 37:18 39:9 211:4 214:15 215:10 222:22 237:22 324:9 377:5 448:18 450:13 452:4,7 452:20
clarification 73:18 458:19 458:21
clarified 297:1
clarify 22:7 35:2 37:6 91:23 101:23 216:20 286:13 464:5
class 80:25 81:25 82:1 84:22 99:14 112:5 259:24 348:13
cleaning 392:14
clear 15:1 75:18 97:23,24 123:12 160:10 164:1 171:7 198:11 227:20 340:3 341:16 342:2 346:8 347:7 348:19 358:13 367:24 398:17 441:22 443:4 445:15 458:25 459:4
CLEAR-IT 269:9,12,13,13 270:2,10,14,15 271:1,5,9 272:5,17,21 275:3,4,14,18 276:19 277:6 277:11 280:18 283:7 284:18 284:20 390:5,6 390:9,16
clearance 97:2 97:13 98:2 99:13
cleared 99:1
clearly 61:22 165:22 183:10 207:3 215:15 259:6 330:25 331:2 339:13 339:15 348:23 348:24 349:1 426:2 440:10 443:21,22
cliff 147:1 280:4
clinic 70:4,24 71:7,11,21 126:25 135:22 137:23 138:18 141:10 261:9 261:10 295:11 295:14,21 299:23 427:2
clinical 6:14 49:25 82:19 83:20 84:9,16 85:9,12,19,25 86:22 87:2,4,5 100:5 106:19 154:12,21,25 155:7,11,13 156:9 159:5 175:14,19 180:3 185:15 199:10 200:9 202:19 204:20 205:9 233:18 238:10,19 239:9 240:13 241:4,8 251:25 325:4,5,10 326:23 332:13 334:9 371:10 371:18,21 372:17 373:7 374:2,24 375:11,19 376:11 378:9 378:20 380:16 380:17 382:15 384:2,19 387:9 388:7 399:19 400:22 402:18 406:2 407:18 408:18 410:3,6 415:19 416:4 416:19,21,22 443:1
clinically 82:17 85:5,7 263:13 264:8,14,21 265:9,12,18,20 265:22 266:13 266:16 392:14 393:2 394:23 395:8,19 396:19,22,24 397:21 398:13
clinician 22:23 159:19 174:19 181:22 182:6 184:25 191:18 199:16 206:19 294:18 297:18 298:11 326:17 397:2 420:14 423:20 440:14
clinician's 421:21

clinicians 252:9 252:16,19
clinics 135:1
close 51:21 300:17 408:6
closely 134:1 408:14
cloudiness 179:5
clumping 180:1
co-administra... 358:15
co-formulation 341:25 342:7 346:12,17 354:24 358:14 358:22
co-investigators 245:3
Cobo 113:14 114:23
Coca-Cola 101:25
cocktail 108:12
Code 42:24
Codes 464:5
cognizant 207:8
collaboration 35:1 80:10 224:23 328:19
collaborative 55:13,14 57:5 208:14 288:3 442:19 443:14 443:16,23 445:19 446:2
collaborators 96:14
colleague 77:13
colleagues 70:1 71:17 154:10 155:19 160:6
collected 84:10
collectively 202:4 205:2
colors 426:15
column 133:24 379:25
combination 58:4 107:21 108:10,24 109:7,16,22 110:12 119:18 123:14 220:13 341:19 342:5 450:10,25 456:5
combine 218:23 219:5 220:10
combined 219:11 365:24
come 17:1 19:5 208:11 217:21 251:5 268:5 278:23 286:11 298:22,24 303:25 416:10 462:8
comes 65:18 77:15 142:15 151:14 191:9 297:15 298:7 321:25 335:14 341:7,10 363:9
comfort 154:1
comfortable 420:19 422:12
comfortably 444:21
coming 191:10 298:3
commencement 461:5
commencing 2:7
comment 22:1 105:10 108:6 159:9 160:9 236:2 281:19 348:23
commented 234:20 235:4,8 254:5
commenting 281:9,12
comments 108:17 160:5 281:4
commercial 216:3,7,13,17 216:21,25 363:21
commercially 166:25 299:20
commit 317:18
committee 238:13
common 72:14 72:14 76:1 171:1 215:5
commonly 80:18 187:5
communicate 288:7
communicated 208:19 440:17 443:22
communicating 71:17
communication 53:22 287:11 443:24
communicatio... 29:18,25 30:2 58:18,23 59:1 287:14 288:13 288:23 289:1,7 289:9,13,19,21 290:4,12,15,19
community 171:8 220:19 261:11 262:2
companies 164:6 187:12
company 17:15 265:11 411:4
comparable 169:8,10 279:24 283:14 379:21
comparative 89:13 417:10
compare 82:18 84:5,5,19,20 85:8 168:25 254:6 278:8 394:12,19 415:12
compared 75:5 253:19,23 263:16 264:9 268:16 269:3 270:11,20,23 274:6 318:25 392:16 393:3 415:5
comparing 82:20 267:5,14 267:20 268:5 268:19 283:14 283:18 394:3 414:25 415:18 416:1,18
comparison 91:9 274:13 279:25 295:11 452:7
comparisons 395:6
competence 142:19
complete 180:7 338:11 462:7 463:15,19
completed 456:25
completely 16:14 37:7 92:12 99:6,7 118:1 122:19 123:2,6 133:13 158:16,24 180:8 227:20 253:7 264:1 267:18 284:15 323:23 325:17 327:11,12 344:11
complex 88:2 422:20
complicated 70:12 76:9 83:22 88:18 110:2 186:20 187:16 282:18 319:3 422:22 423:9
complication 393:25
components 324:9
composed 317:19
composition 426:25
compound 92:3 164:19 166:12 188:13 228:4 243:21 255:22 266:6 267:15 297:19
compounded 253:8
compounding 253:11 256:1 257:2,4,5,15
compounds 116:16 267:21
comprehensive 122:25
comprise 220:3 349:15 350:19 353:25
comprising 38:10 349:18 350:23
computer 155:18 306:11
con 102:2 105:20,20 181:8 216:23 303:18 395:24
concentrated

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 473 of 524

367:25 424:11
concentration 100:12,15,21 101:2,4,8 102:1,4,10,10 104:19,25 105:16,21 106:11 183:8 190:24 192:2,6 192:16,22 193:3,6,11,20 193:24 194:7 194:16 195:9 196:16,18 219:15,17 221:25 223:15 224:15,19,25 236:12,24 243:6 252:3 257:3 286:5,15 286:24 293:18 296:12 301:14 301:21,24 302:8,24 303:6 303:19 304:3 304:11,16 305:24 313:5 314:20 315:7,9 316:1 318:23 319:18,20 320:10 321:13 323:13 328:1 329:18 330:20 331:21 333:2 334:18 335:8,9 335:11,17,24 346:11 354:17 355:25 356:2 356:23 362:13 363:2,7 364:14
concentrations 36:6 104:12 106:3 221:22 297:23 302:6 302:10,13,17 302:18 313:20 313:25 317:12 319:6,21 320:11 322:3 330:14 331:17 334:6,8,22 335:1 336:23 343:9 354:18 356:9 359:8 360:13 361:1 415:1,18 416:2
concept 192:12 217:12 342:24
concepts 192:5
concern 163:6 179:19 186:8 191:1 409:23
concerned 326:19
concerning 142:11 179:11 186:12
concerns 81:9 125:19 152:7 190:19
concert 175:25
conclude 34:17 107:9 340:7 346:19 398:12 446:12 457:5
concluded 266:12 396:18 397:9 398:13 409:5
concludes 329:25
conclusion 34:20 35:15 36:10 39:12 56:20 91:14 99:25 120:23 121:18 122:15 123:9 133:11 134:18 199:19 202:8 202:22 217:1,6 262:21 263:18 264:17 272:5 279:22 321:10 323:5 337:17 346:5,16 391:14 392:1 398:10 408:4,7 428:24 429:12 429:14
conclusions 271:10
condition 233:15
conditions 76:11 76:19 149:7,10 317:2
conducted 2:5 141:7 283:3,6
conducting 197:22
conferences 20:13 71:16
confidence 267:23 325:7 325:11
confine 78:9
confined 87:15
confirmation 137:23 138:5 138:22
conflict 322:9,12
conform 444:16 464:6
confused 57:16 320:7 334:3 438:8
confusing 40:21 61:5 317:11
confusion 358:25 359:5
connect 181:15
Connolly 3:15 4:5 9:21,23,25 11:10
consent 462:22
consequence 203:22 233:13
consider 22:1 62:11 67:15 114:3 116:5,22 117:6,20 118:1 118:16,22 119:5 120:8 142:22 147:3 185:20 186:11 206:5,25 207:1 210:25 213:1 215:17,21 218:2,9,14 241:17 242:4 244:1,5 251:16 251:18,21,24 255:6 256:9 258:19 282:4 285:18 299:8 299:11,13 321:17 326:18 328:21,22 344:5,15 362:4 381:1 413:24 414:6 417:20 448:13 454:3
consideration 46:8 119:7,9 406:19
considerations 241:22 355:22
considered 50:4 50:14 73:14 75:9 76:1 87:4 113:12 114:9 182:23 183:3 206:1 213:25 214:7 223:18 227:17 272:12 279:9 299:4,8 300:1 344:13 344:20 362:5 380:25 381:3,4 385:9,15 432:5 432:7 445:3 452:13
considering 431:25
consisted 445:21
consistent 51:14 99:16 382:23 383:4 384:12
constant 422:1 424:2
construction 244:12 255:5
contain 156:8 177:24 335:25 336:15 345:8
contained 28:11 456:6
containing 181:25 182:10 321:13 356:15 356:17 420:1
contains 184:11 325:1 371:20
contaminated 184:6,19
contemplating 117:18
content 196:1 210:25 211:22 449:3,19
contents 181:8 211:21 397:11 447:23 449:9 449:12 450:4 450:16
context 71:25 94:4 101:16 105:5 118:9 144:14 228:12 260:16 261:20 326:23 337:15 339:10 345:13 348:18 357:21
continue 93:17 93:19,20 95:11 149:12,14
continued 93:15
continues 46:1 134:2
continuing

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 474 of 524

contradiction 350:4,12 395:19
contrary 398:10 398:12
control 72:3,6 72:12 168:2 421:2,7
conveniently 295:20 424:15
conventional 73:10 75:12 130:11
conversation 52:20 53:9,14 57:4 59:13 60:12 61:18,18 62:2 73:17 86:15 151:18 196:2 208:22 287:5,9,10 291:6,8 292:8 293:3,12 294:8 294:10 350:1 443:23 445:16 445:22
conversations 20:10 33:18 59:2,18 154:8 221:20 287:24
conversed 51:19
conversely 192:19 264:6
convert 319:5
converting 424:23
convey 451:20 452:18
conveyed 57:3 58:13 199:7 375:25 437:16
conveying 425:12 450:23
convince 143:23
convinced 143:23
cooked 153:11 153:17
copies 437:10,12
copy 39:16 40:5 62:21 63:9,12 79:17 209:7 247:15 437:5 438:16,25 439:17 462:9
Copying 462:21
Copyright 462:20
cor 416:3
cornea 98:17
corneal 120:14 122:21
Cornell 68:23 70:15
corner 31:13 158:21 419:22
corporate-spo... 283:9
correct 12:14 13:21 23:3 27:21 28:18 29:5 30:17 35:8 36:11 41:23 42:14 47:25 49:17 51:1,12 52:13 52:17 64:14 74:19 81:1 102:13 108:25 129:14 132:14 132:23 158:9 167:1,3 170:2 175:8 190:7 192:17 193:4 195:6 199:12 205:5 211:23 214:11 216:1 226:25 229:11 243:10 246:23 246:25 271:3 272:18,22 273:3,10 281:10,22 289:10 291:14 297:11 302:4 308:24 311:21 312:21 313:9 313:21 314:2 316:18 329:21 338:7 341:13 345:24 353:6 359:11 360:1 365:10 375:6,9 375:12 377:13 380:9 382:17 383:17 389:18 390:13 396:22 399:16 400:25 400:25 403:25 407:13 414:18 422:4,14 423:16,23 430:21 431:5 434:24 437:7 437:18 441:1 441:11 447:17 450:18,19 451:15,16 452:5 459:11 463:14,19 464:7
corrected 230:1
correction 229:18 459:7
correctly 43:2 50:7 142:2 452:3
cost 264:23
counsel 4:3 9:16 10:2 17:23 20:11 21:1 32:16 35:1 37:18 39:15 41:19 45:13,21 58:19 79:18 90:12 95:2 123:24 124:18 199:7 207:6 210:22 212:10 247:14 288:9 288:10 289:13 303:1,5 307:1 310:8 372:8 411:15,16 419:17,19 435:25 436:6 437:16 440:18 441:25 442:13 442:24 443:8 443:24 444:3 444:11 446:10 447:17 448:10 448:23 452:12 453:19 457:25 458:15 459:16 459:17 461:16 461:18 462:10 462:13
counsel's 435:11 453:7 454:21
counselor 206:18
count 120:15 122:22
country 406:12
couple 22:11 225:2 324:8 453:8 454:20
course 22:9 56:6 86:6 102:20 131:1 151:16 167:21 171:3 182:5 293:14 297:16 328:24 344:7 348:2
court 10:11 14:1 14:8 15:16,17 79:10 128:21 207:8 208:2 433:14 434:2 461:22
court's 31:23
cover 131:12
covered 58:19
cracked 178:23
cre 267:22
create 75:23 137:1 157:22 202:10 293:23 297:5,8 328:20 427:13 439:14
created 138:12 174:13 433:9
creating 19:8,24 137:24 166:5 293:17
creation 56:9 327:23 410:23 442:1
credence 141:6 141:22
credentialed 75:24
credibility 157:3
cross 13:24 403:14
crossed 361:15
crossing 86:11
CRR 1:22
crummy 158:18
cube 278:22
cumulative 107:20 393:24
curated 157:5
cured 144:20
current 326:13
currently 68:25
currents 286:1
cut 275:11
CV 74:13 77:24 129:7

D

D 227:17,19
D'Amico 1:14 2:5 5:6 6:5,5,9 6:13,18 7:5 9:15 10:10,24 11:6 29:20 31:12 58:16 79:11,11 95:22

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 475 of 524

96:5 106:18,24 117:10 121:21 124:14,23 125:9 133:10 201:5,6,21 202:2 203:11 206:5,13,15 207:13 247:7 289:16 306:23 368:6 446:9 447:6 452:24 453:19 457:23 458:3 460:8 461:6 462:2 463:8 464:4,25
D.C 1:24 463:3
daily 169:3 193:25
daltons 422:21
damage 91:10 232:25
damaged 93:18 179:2
damaging 105:13
DARPin 164:19
data 86:20,21 133:21 141:4,5 142:22,23 143:6,7 144:15 154:15 155:3,8 156:8 157:1,4 157:19,24 158:4 159:4,19 159:22 160:3,5 160:6,7,8 166:18 174:3 175:14 218:7,8 218:13,14 245:23 246:1 256:3,5 263:25 264:25 267:24 268:16 282:12 282:14,22 283:2 284:8,16 286:2 325:4,5 325:10,20 327:1 377:16 379:17 381:1,8 381:19 382:16 395:12 396:7 404:25 406:18 406:23 407:10 407:12 414:21 414:22 415:9 423:5
data's 327:2
date 2:8 9:9 24:20 52:2 53:8 59:14 60:4,11 79:14 96:1 106:22 125:1 144:25 148:15 236:20 247:10 381:24 461:12 462:3 463:9,23,25 464:3
Dated 461:25
dates 52:24
day 14:4,7 25:21 42:4 43:14 46:20 62:2 69:6,8,11,14 69:18,21 71:3 134:1 144:22 153:2 265:2 266:18 295:19 391:23 445:22
day-to-day 69:3
days 22:11,18 25:4 71:7,11 71:12 273:22 276:12,14 391:6,7
DC 3:20
dead 94:12
deal 262:1 295:4
dealing 346:19 374:16
debates 160:8
decades 150:24 170:25
December 6:11 95:24
decide 186:17 187:23 252:9
decided 140:8 314:16 356:13 362:21,24 434:3
decimal 225:3
decision 187:21 285:10 418:3 419:3
decision-maki... 361:3
decisions 154:12
declaration 12:1 12:10,12 13:12 13:16 18:23 19:8 21:20 24:6,9,21,25 25:6,12 26:3,5 26:10,14,17,18 27:3,4,8,10,19 28:12,12,16,17 29:10,12 30:7 30:13 39:20,22 39:23 40:16,22 41:4 43:10,12 46:16,21,25 47:20 48:16 49:21 51:22 52:8 53:14,18 54:5,15,17,20 55:17,19,24 56:12,19,21 57:2,14 58:1 58:14,25 59:20 60:6,15 61:17 61:21 63:5,8 162:14 186:14 194:10 195:15 195:19,25 196:7,12,23 199:22 202:17 203:24 208:18 209:1,12,19 211:18 213:9 213:16,19,20 215:25 216:8 227:9 243:17 274:18 291:20 291:23,25 307:11 313:15 334:14 351:23 352:14 353:13 353:15,20,22 372:1 373:2,3 374:2 375:17 378:9 380:23 383:15,22 387:7 389:7 390:9 393:12 397:7,18,25 398:8 412:13 425:20,25 429:18 434:22 437:6 439:12 439:14,19 440:24,25 441:7,15,16 442:9
declarations 433:10
declare 42:11,15
decoy 227:1,3,5
decrease 224:6 405:8
decreased 186:8
decreases 393:22,24
deep 295:17
defend 322:13
defer 95:7 207:10,13 222:14,15 286:23 427:16
define 74:24 93:7 94:3 118:23 144:9 212:16 347:10 458:20
defined 175:7 198:13 199:20 201:7 203:7 343:25 446:4
defines 348:14
definition 21:9 73:13 75:14 76:13 78:14 93:23 104:18 121:25 182:21 200:2,18 203:18 204:5 204:12 210:3 212:9 338:11 344:6,15 346:1
definitive 90:23
degeneration 17:7 20:2 33:9 36:15 58:7 77:8,23 78:2 147:12 165:16 165:24 230:24 248:20 249:23
degree 63:21,25 83:23 91:10
degrees 457:15
delicacy 84:18
deliver 190:22
delivered 224:7
demonstrate 376:11 378:10 387:10,17,19 388:7,24 389:3 389:8,9,11 392:2
demonstrated 110:20 165:23 186:4,6 412:24
denote 7:10
dense 360:5 368:9
dep 165:22
depart 68:18
Department 68:24
depend 117:24

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 476 of 524

145:25 187:9 263:24
depended 112:4
dependent 118:5
depending 69:8 73:12 172:13 187:13
depends 74:23 176:16 422:24
deponent 9:14 462:8,10
deposed 11:16 13:5,8 27:23 28:2,3 432:20 433:8
deposition 1:13 2:4 8:1 9:11 11:13,21 19:19 21:14 28:6 52:16 428:2,11 428:14 460:13 462:3,13 463:9 463:12 464:3
derives 320:24
describe 152:23 156:14 184:3 196:24 212:13 238:2 271:10 271:16,18 274:11 311:23 342:5 344:2 358:21
described 104:19 148:15 175:4 189:12 191:22 208:13 213:22 214:4 215:14 237:9 271:15 274:16 274:18 288:3 307:19 343:21 362:16 402:14 405:9 406:2 426:1 432:25 445:14
describes 219:22 277:10 339:12 341:18,21,23 341:25 344:3 358:16,20 372:23 425:1 429:1
describing 84:17 148:3 154:25 182:17 228:13 248:19 289:14 290:19 343:8 345:15 346:9 346:10 347:7 358:2,6,14 400:19
description 6:4 7:4 205:17
descriptive 407:6
design 156:16
designated 104:9
designation 75:2 75:12
designations 75:23
designed 243:19
designer 174:7
desirable 309:14
desired 332:18
detachment 77:11 161:6
detail 21:4 73:19 213:16 219:23 329:8 358:18 360:6
detailed 240:24
details 73:23 138:12 142:8 143:19 410:16
detect 88:10
detectable 132:19
determinable 401:17
determination 98:11 175:5
determine 32:24 33:23 34:20 53:17 91:9 92:7 114:24 149:5 173:15 174:19 258:11 258:12 328:15 435:2 436:15 441:4
determined 99:12 105:25 113:17 257:16
determines 100:14
determining 89:15 118:14 142:22 278:14 280:11
devastating 188:14
develop 108:13 249:17 451:2
developed 215:7 250:15 293:14 424:13 437:14 443:8,13,14,15
Developers 272:25
developing 442:25
development 198:4 203:1 231:16 232:3,9 366:20
devices 171:5
devoid 260:16
diabetic 36:16 36:16 147:12
diagnosis 76:21 77:18
dictating 116:24
die 93:21 247:20
Diego 3:8
differ 76:4 101:3 103:12
difference 78:16 223:3 227:18 229:3,20 245:10 263:14 264:8,15,22 266:14,25 279:1 392:15 393:2 394:21 396:19,24,25 397:3,22 398:17
differences 81:15 86:12 104:24 211:2 212:14,17,19 213:11 214:1 275:6 281:20 413:25 414:7 414:12,16 418:6 448:16 452:13
different 21:11 22:20 40:1,9 61:20 66:18 81:14,16,17,18 81:18 82:17 83:2 84:21 85:5,7,11 86:12,13,13 92:4,5,6,12 99:7,8,20,20 102:24 104:11 104:12,20 106:3,4 114:6 125:21 134:21 139:3 141:6 162:2 165:12 165:13 170:4 170:13,20 171:16,16 172:13,13 183:13,18 186:21 227:13 239:24 245:13 253:23 255:6 257:7 258:5,24 262:15 265:13 267:18 283:10 283:10,11,16 298:8 309:5,5 322:3 324:9 327:3 329:4 333:14 343:19 368:4 377:2 397:3 402:4 408:21 418:17 418:17,19,20 424:24 435:18 440:21
differently 83:3
difficult 361:23
difficulties 86:17
difficulty 135:6
digital 1:23 9:8 41:16,17 462:19,20 463:1
dilution 131:17 135:5,6 137:1 138:12,13,13 184:22 409:11
dilutions 136:4 137:25
direct 111:7 268:22 282:21 374:23
directed 231:13 420:6
direction 8:3 76:13 265:13 441:22
directly 225:18 283:14 289:22 290:16
directs 231:24
dis 303:14 356:14
disagree 127:11 127:19 133:14 135:18 139:13 140:19,25 146:7 262:24

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 477 of 524

428:21 429:11 429:13
disappointing 158:23
discharge 153:1
discipline 66:15 74:25
disclose 38:22 305:17 312:10 314:12 428:3
disclosed 38:9 39:3 220:21 224:17 237:13 237:21 302:19 308:19 319:15 322:5 332:10 332:20 334:19 334:25 361:25 368:22 427:20 429:23 430:19
discloses 219:14 301:15 302:17 303:6 304:17 305:22,23 311:4 320:18 330:11 333:20 335:17 349:18 350:7,8,9,22 351:4,22 353:2 358:1 360:14 366:6
disclosing 38:15 352:15,23
disclosure 306:5 310:19,21 323:18 334:21 338:3,5 352:11 353:13 355:8 359:6,7 361:10 361:14,16 428:18 430:17
disclosures 285:16 307:15 314:19 321:5 322:16 323:6 330:2 352:10
discomfort 421:1
discount 267:9
discouragement 388:20
discover 214:24 224:19
discovered 215:3 224:10 224:15
discovery 425:6
discuss 84:16 124:17 146:10 306:25 307:3 375:11,12 445:1 449:18 453:4
discussed 59:15 89:1 122:21 176:23 293:13 365:5 377:16 397:20 419:2 445:20
discusses 276:18 277:5
discussing 73:3 105:5 130:4 131:7,16 146:10,11 270:17 294:13 294:14 357:20 359:19 419:4 424:21 451:10 456:4
discussion 33:8 50:1 51:3,5 109:3 110:19 119:16 148:25 151:24 287:1 409:24 452:25
discussions 19:6 33:17 154:9
disease 76:19 139:21 148:3,4 187:14 231:2 254:1
diseases 67:13 68:11,12 187:14 226:23 233:1 254:2
dismiss 299:9
disorders 49:24 49:25 197:18 197:23
disparity 115:24
dispositive 117:4,21 118:17
disproving 322:10
dispute 61:11 398:16 452:4
disqualify 361:19
dissuaded 320:3
distinct 22:2 75:5
distinction 108:21 184:8 202:10 206:21 338:9 343:2 348:11,12
distinguishing 110:24 255:9 255:13,16 349:2
distracted 229:16
distribution 96:23 115:9,11
disuse 241:13
divide 315:18 316:19 331:24
divides 225:1
dividing 243:8 297:14
DME 37:12
doable 354:23
doctor 15:3 90:15 94:7 95:8 173:19 197:16 226:17 256:20 262:20 276:6,21 451:9 454:19
document 7:11 21:15,17 31:15 31:18 40:4 54:4 56:6,9,25 61:7,15 79:7 79:22 80:3,7 84:15 95:19 96:4 106:16 110:10 113:1 123:22 125:3,8 125:15 139:4 140:13 195:1 223:9 229:22 235:4,5,9,10 235:21,24 236:1 247:4,20 248:1,4,10,11 248:12 249:5,9 249:11,18 252:24 270:7 271:20 272:2 275:19 276:6 276:20 277:2 291:11,12 305:2 329:15 368:7,10,12,14 368:17 369:6 369:20,23 370:2,10,14,24 372:25 419:10 436:7,22 439:23 456:20 456:24
document-wise 353:17
documentation 143:11 223:23 224:9,11
documented 77:24 109:6 119:17 146:9 157:5
documents 8:8 13:15,19 20:7 24:3,5,8 38:8 50:5,11,14,22 95:16,17 210:8 289:3 374:15 433:8 439:1 442:1
DODAC 241:8
doing 47:24 58:21 71:13 73:2 130:2 229:15 317:2 318:4 384:6 456:21
dollars 179:1
domain 332:19
Don 10:10
Donald 1:14 2:5 5:6 9:14 10:24 201:4,6,21 202:2 203:11 206:5,13,15 461:6 462:2 463:8 464:4,25
door 266:25
dosage 83:4,16 88:12 132:18 141:14 142:9 149:2 184:22 219:19 248:23 265:14 307:17 384:1 393:20 394:5,14 396:10 398:20 418:19 458:25 459:5
dosages 115:5 127:5
dose 19:25 80:14 84:9,21 89:8 90:11 92:14 97:17 99:17 100:6,19,21 101:4,7 104:13 112:1 118:3,15 126:17,23,24

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 478 of 524

126:24 127:13
127:19,22,22
131:24 133:20
136:11 139:6
141:25 178:1
187:23 189:11
189:23 192:15
192:20,25
193:7 220:14
224:12 225:2,5
236:16,16,20
236:22,24
237:5,8 240:2
240:4,9,16,17
241:18 242:2,8
242:9,11
249:17,24
250:1,4 252:10
252:16,17,25
254:16,21
256:15 257:22
258:1,20 259:7
260:9,10,25
261:3,18
262:10,14
263:6,15,17
264:7,10,19,20
265:1 266:4,13
268:3,5,6,17
268:20,24
269:4,5,19
270:12,12,20
270:20 271:12
271:13 274:13
274:14,21,22
274:23 278:9,9
278:15 280:12
281:1,5 282:5
282:17 283:25
284:2,5 285:8
285:14 294:6
294:19 296:2
296:23 297:5,9
298:3,6,21
301:13 308:21
309:19 312:8
312:14 313:12
314:19 315:7
315:11,18
316:1,14,16
319:6,25
320:17,24
321:24 324:15
326:12,13,15
326:17 327:23
328:5,23 329:6
329:20 330:11
330:22 331:1
332:1,7,9
333:6,13,16,17
335:8 354:15
362:9,10 363:8
365:19,21,23
367:11 368:3
369:5,16,24
370:6,10,11,15
371:1,12
372:20 373:9
374:4,15 375:1
376:12,21
377:8 378:11
380:1 383:6
384:14 385:24
387:11,24
388:8,13,18,24
392:13,17
393:1,4 394:20
395:2,6,16,22
396:18 397:21
399:14 400:8
400:19 401:7
403:19,23
404:6,7,8,9,13
405:14,23
406:1,20
407:20,25
408:8 412:22
412:22,24
414:8,9 415:7
415:19 416:19
416:22 417:10
432:6,7 445:15
453:21 454:9
454:10,16
456:11
dose-ramping 254:7
dosed 83:3,14
117:15 273:1
300:12 357:6
401:21
doses 74:12
82:17 84:20
85:5,7 91:3
92:5 115:25
123:14 171:17
220:19 240:13
240:20 241:5
253:23,24
256:3 261:21
267:7,11 273:7
274:5 277:13
278:3,3 281:21
286:3 309:6
313:20 314:13
318:20 319:14
324:21 325:12
325:24 333:14
333:21 374:12
386:16 388:21
393:14 399:19
405:17 415:5,6
415:12 416:5
417:6 418:9,11
dosing 83:20
84:17 86:22
112:3 114:10
115:12 116:16
116:20,23,24
119:10 143:24
197:19 234:23
236:5 241:15
241:23 250:2
256:1,10
257:10 267:24
double 121:8
401:5 409:11
417:24 455:23
doubled 102:5
doubly 417:22
dozen 11:17,18
385:22
Dr 9:14 10:4,10
11:6 16:6,9,12
21:2 24:12,13
25:12 26:3,17
27:4,9,22 28:9
28:11 29:14,20
29:25 30:8
31:12 50:2
51:4,9,19 52:7
52:15,19 54:5
55:2,25 56:3
56:11 58:12,16
59:4,9,10,12
59:22 60:12
62:21 76:5
77:9,12,16
96:5,13 106:24
117:9 121:20
124:13 125:9
133:9 176:1
195:8,17,21,24
196:2,9,15
206:13,14
207:13 208:7
208:20 222:15
245:23 246:6,7
246:15,22
277:5 286:23
288:1,11,16
289:9,15,22
290:4,13,16,20
291:4 294:3,4
294:8 296:22
297:25 298:1
301:3,6 306:23
368:6 379:11
423:15 427:17
428:2,16,22
429:12 434:18
435:11,21
437:1,15
438:12 439:18
440:3,9,24
441:8,21
442:15,17
443:15,18,25
444:3 446:9
447:6 452:24
453:19 457:23
458:3 460:7
draft 63:9,12
209:7 434:22
435:22 436:9
437:12
drafting 30:7
drain 98:19,21
draw 177:1
264:17 285:7
338:9 343:2
348:11,12
draw-up 177:18
drawing 178:4
206:22 258:13
297:19
drawn 177:4,22
drips 296:13
drive 115:12
163:7 169:4
driving 162:13
drops 130:16
131:2,14
136:20
drug 24:13
74:15 81:25,25
84:20,21 87:16
89:17,24 90:6
90:8 94:12
96:23 97:23
99:1,4,4,8,15
99:18 100:13
100:15 102:12
104:13 105:5,9
105:14,17,19
106:10,13
107:23 108:6
109:20 110:7
110:20 111:21
114:5 115:4,15

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 479 of 524

115:17,20,25 118:15 119:2 122:24 123:2,5 128:4 129:9 132:8 142:9,11 143:19 144:19 147:15 148:1,6 148:17 153:13 162:16 164:12 165:17,19,22 166:16,24 170:22 171:21 172:14 173:14 173:25 174:1,6 174:9 176:2,6 178:9,10,20 180:20,23 182:9 183:9 187:24 189:1,8 191:1 225:14 238:16 240:25 241:13,20 257:7 259:8,23 262:6,16 263:23 265:10 265:24 283:20 285:9 295:8 325:6 366:20 367:1 371:12 372:19 373:8 373:22 374:4 375:1 380:2 381:10 383:7 384:14,22 385:25 386:24 388:13 394:5 394:15 395:9 396:10 397:5 414:10,14 420:18 421:19 424:22
drugs 70:20 71:20,22 72:3 80:25 81:14 82:6,9,20 83:1 88:12,19 89:3 91:13 96:22 98:5 99:2,20 100:3 107:12 108:4,24 111:25 112:5,5 112:8,12,14,18 112:18 114:6 118:9 123:18 134:21,22 135:2 144:12 155:5 161:20 168:19 170:12 170:14 175:24 183:17,20 197:19,21 225:6 242:7,9 242:10 259:24 260:12,19 266:9 280:2 283:17 299:21 300:11 339:9 348:8,13 356:21,22,25 418:16,17 427:1 431:23 432:6
ducks 411:22
due 147:10 445:23
duly 10:25 461:6
durability 263:15 264:9 266:7,15 383:8 384:15 386:1 386:15 392:16 393:3 394:6,22 396:12,20 397:23 398:6 413:1
durable 394:16 413:4
duration 106:11 164:4 167:5 171:11 186:7 187:6 241:20 242:2 254:17 254:23 257:22 258:2,22 259:7 259:10 260:9 260:11 261:12 261:19 262:4 262:11,15 263:7 265:5 266:10 268:4 268:18,21 269:3 274:12 274:22 278:16 279:4 280:13 280:25 282:6 284:3,6 376:13 377:10,12 378:12 380:2 384:4,9 387:12 387:25 388:9 388:14,25
Dutch 102:25
dye 426:10,22 427:8
dyes 420:1,8,11 425:9,16,24 426:13 427:22

E

E 6:2 7:2 226:10 226:10 412:5,5 412:5
eager 171:10
earlier 18:5 28:14 51:18 52:14 54:2 127:4 128:15 129:15 176:23 247:3 300:6 339:22 417:9 432:19 437:10 447:8 448:24
earliest 87:14,18
early 46:16 345:22
ease 109:19
easier 275:18 295:3 423:2
East 163:8
edema 36:16
edge 98:16,17
editing 71:16
editorial 157:21
educate 155:24
educated 251:4
education 49:22 203:25
effect 61:9 88:13 93:9 96:10 132:20 180:3 228:7 233:18 253:25 257:23 258:2,22 259:7 259:11 260:9 260:11 261:13 268:17,18,19 268:21 269:3 274:12 279:4 279:14 281:1 282:22 383:8 384:2,4,15 385:25 386:14 394:6,15 396:11,21 398:5 406:24 418:19
effective 137:2 147:16,23 155:6 260:25 376:23 383:7 384:14 385:24
effectively 102:4
effects 88:19 91:1,18,19 93:4 116:17 147:11 148:12 175:18,18 181:24 182:8 242:10 260:22 374:19 384:1 407:4,7 418:18
efficacies 81:18
efficacious 188:13 412:25
efficacy 119:2 144:15 151:6 163:22 164:4 165:18,22,23 167:22 171:11 180:13,17 186:7 187:7 224:8 241:19 242:3 254:23 261:13 262:3 263:14 264:9 264:20 265:3 266:14 274:24 275:14,14 377:9,12 383:9 384:8,16 386:1 386:14 391:18 392:15 393:3 394:6,16,22,25 396:12,20 397:22 398:6 414:17
effort 55:13,14 204:2 368:19 368:21 369:3 443:15
eight 22:16,19 23:20 71:9 163:10 275:5 275:12,15 278:2,25 279:8 296:25 379:20
eight-week 275:5
either 77:15 78:4 97:20 181:5 186:6 187:3 274:16 312:23 357:1 358:11 361:23 376:22 377:9 395:7,21 421:16
either/or 160:9
El 3:6
elderly 163:4 169:22

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 480 of 524

electron 110:13 112:25
electronically 462:21
element 29:13 56:20 120:7 148:6 296:8 418:2 427:6
elements 28:10 122:20 135:17 142:21 146:9 147:11 176:25 285:10 288:14 295:7 332:20 332:22 441:23
elevating 366:2
elevation 191:5
eliminate 263:22 437:25
else's 287:20
elucidated 147:14 151:2
eluding 100:3
elusions 106:4
EMA 372:4
email 3:10,22 53:12,17,23 434:20 435:1,5 435:16 436:16 436:21 437:10 437:21,22 438:10
emailed 438:12 438:14,18,19
emails 19:4 59:2 435:14
embodied 381:4
embodiment 307:18 308:1 309:2,3,4 312:17 316:4,8 349:18 350:23 351:4,24
embodiments 316:16 320:19 331:6 336:13 340:13 345:6 346:16
Empire 223:13
employed 177:20 307:15
employee 461:15 461:17
emulsions 357:2
en 168:2
encountered 82:19 85:9
encouraged 266:3
encouraging 267:2,3
endocrine 149:9
endophthalmitis 73:6 74:3 128:10 130:7 136:2,5 140:4 255:4,24
endothelial 120:15 122:21
endpoint 133:15 275:5
engaged 18:9 19:2,7 20:10 32:16 33:16 37:17 210:16
enormous 36:20
enrolled 408:2
ensures 258:14
enter 355:22
entered 100:22
entire 71:18 86:9,10 88:17 328:25 347:15 351:12 355:3 400:14
entirely 44:16 44:19 110:18
entirety 342:9 346:20 449:22
entitled 247:21
entity 167:11
enumerate 23:8
environment 172:14 407:7
epidemics 255:24 267:13
episodes 255:4 255:23
epithelial 89:18 89:25 90:7 91:19 93:5,6 94:13
epithelium 87:17,23 88:1 88:15,23 89:5 112:24 115:24
equal 120:9 190:9 265:2 300:6 395:7
equally 77:9 173:6 267:6
equals 312:19
equate 308:21 309:1,4,5
equates 429:25
equivalence 395:16
equivalent 121:2 121:4 279:11 370:16 395:21 416:19
errata 462:12 463:18 464:1
erroneous 344:12
erroneously 407:20
error 131:17 184:22 351:7 351:10,19,20 409:11
errors 137:1 351:22 464:7
escalating 417:10
escalation 89:9 326:12,17 404:6
ESQUIRE 3:5 3:16,17,18
EST 1:19 2:8 9:2 460:14
establish 231:17
established 147:25 148:14 324:1 333:17 381:13
establishing 417:11
estimating 116:5
et 21:7 35:25 59:3 75:25 81:19 86:14 115:10,10 122:23 127:1 138:1,18 143:13 184:23 187:16 234:15 266:10 282:13 286:25 287:3 289:5 295:7,7 295:22 317:13 317:17 342:1 346:17 409:22 410:12,19 413:4 418:20
European 6:18 124:24 372:3
evaluate 32:23 154:15
evaluated 34:25 400:23
evaluating 92:3 175:11 452:19
evaluation 141:3 159:17
evaluations 273:8 277:15
evening 5:11 149:7
event 297:2 304:1
events 394:7 398:7 407:9
eventually 16:2 437:4
everybody 144:21 215:5 265:7
evidence 1:23 9:9 100:11 107:13 151:22 211:4 214:14 215:9 254:20 268:2,12,22 282:21 284:25 285:1,6,19 286:5,15 321:22 363:13 363:14 374:7 374:10,11,23 376:1 389:21 448:18 462:19 462:20 463:1
evidenced 99:3 377:15
ex 164:2 279:6 391:21
exact 7:11
exactly 19:10 33:19 40:4 83:10 415:7
examination 5:6 11:4 151:17,17 152:11 447:4 453:7 458:1 461:5
examine 177:8
examined 11:2 88:13,16 134:4 463:11
example 38:2 75:3 77:7 91:18,23 92:2 96:24 119:2 120:14 138:13 148:11 162:3 166:11 171:1 186:24 198:6 203:4 215:2

223:12 334:14 340:18 341:1,7 341:8 352:3,5 359:13,25 360:2,25 361:4 420:20 438:16 449:7 458:22 459:6
examples 105:7 173:9 330:17 330:18 336:22 336:24,25 340:4,22 342:21,23 359:20,24 360:11,19,23
exceed 415:19
exceeded 277:22
excellent 274:1
exception 70:25 442:10
exceptions 261:8
excess 177:24
exchanged 433:9 435:13,13
exchanges 20:11
excipients 427:17
exciting 40:6,8
exclamation 86:6,8
excluded 433:14 434:1
excluding 216:16,18
exclusively 76:12 444:18 445:1
excuse 17:12 39:18 48:5 88:14 90:2 93:5 128:9 132:1 155:12 159:19 185:22 199:2 210:10 213:10 221:21 222:15 225:12 250:11 253:20 255:11 271:12 273:14 277:24 283:25 301:13 328:7 331:24 339:2 358:19 395:15 399:23 402:19 444:22
exempli 454:12
exhibit 6:6,10,14 6:19 7:6 31:23 40:10 54:14 55:16 79:9,11 79:16 80:7 95:21,22 106:18,24 124:21,23 153:19 244:24 245:19 247:7 272:8 275:20 275:25 276:4 304:24 368:5,5 371:20,23 372:2,16 374:9 375:3,10 376:2 377:20 378:5 390:11,22 391:10 394:1 396:13 398:22 398:23 402:15 419:8 440:23 447:21 453:17 454:23
exhibits 5:5,16 7:9 245:5
exist 56:18 224:20 254:8
existed 56:6 417:19 418:1
existing 167:6 427:4
exists 177:14 228:15,16,17
exit 98:24
expansive 154:18
expect 81:7 92:17 140:13 160:24 258:23 260:10 274:21 274:23 413:20
expectation 116:7 120:19 120:20 121:15 122:13 123:5 137:11 152:5 219:7 221:6,9 221:16 258:3 262:13 364:5 366:23 412:21 413:6 418:10 451:11 456:9
expectations 123:11,18
expected 99:22 139:7 259:10 263:5
experience 49:22 72:23,25 73:1 104:12 128:17 129:3 129:25 130:1,2 178:15 198:3 203:1 239:14 241:10 328:25 356:20
experienced 277:20
experimental 6:15 96:9 106:20 107:1 375:22
expert 10:9 12:1 12:2 17:5,5 21:2 24:14 32:17 34:13 58:8 67:16 228:11 354:25 423:14 441:15 445:22
expertise 168:17 176:2 181:20 201:17 222:12 426:2 429:8
explain 20:20 152:2,14 153:5 160:21 161:11 278:7 310:18 397:8
explained 328:3
explaining 184:16
explanation 151:19
explicit 338:15
explore 171:15
exploring 164:3
exponential 422:19 424:4
exposure 106:12
express 189:22 194:5 462:22
expressed 186:13 192:7
expresses 184:25 459:5
extensive 20:17 73:1 130:2 410:25 452:25
extensively 20:6 74:14 87:1
extent 289:21
extrapable 414:13
extrapolate 259:23 414:21
extrapolating 413:18
extreme 206:23
extremely 103:13 104:7 105:12 241:10
extremes 361:22
exudation 165:16
eye 49:24 67:3 71:23 72:4,8 72:11 96:11,17 96:19,19 97:1 97:3,6,14,17 97:19,23 98:1 98:9,19,21,22 98:24 99:1,5 100:3,4,7,24 101:1 105:11 106:5 107:7 109:9 110:8,15 110:21 111:6 119:20 128:5,8 132:9 142:12 152:8,23 153:15 154:2 169:6 170:1,6 170:15 173:3 173:11,16 174:21 175:6 176:12 180:16 182:1,13 184:1 184:15,21 188:23 191:11 197:18,23 226:24 228:15 228:17 229:10 230:14 231:16 232:4 233:1,7 233:21 243:24 248:16 253:13 255:2 258:15 260:20 266:7 295:24 299:23 300:8 325:8 376:13 378:12 387:12 405:6 420:22 421:12
eyes 70:21 100:10 106:1 113:22 114:17 136:3 232:13 232:16 426:10
eyesight 168:12
Eylea 187:9 188:3,3 218:23 219:5,11,19

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 482 of 524

220:14 225:7 225:11 236:13 237:5,8 370:6 370:15 412:22 415:13 427:5

F

F 226:10
fabrication 356:2
face 386:9
facilitate 426:15
fact 75:10 81:16 120:21 142:14 142:16,16 147:25 148:14 198:15 204:17 217:4 234:22 267:1 279:10 282:11 302:21 304:18 326:21 339:13 360:24 361:17 362:17 396:17 398:18 403:6 409:20
factor 99:14 119:1,3 148:22 227:19,23 230:4,9,13,18 230:19 231:8 232:16,18 233:7,20 261:18 421:20
factors 98:3 116:19 118:24 119:6 120:16 148:23 187:21
facts 464:6
factually 204:16
faculty 68:16
fail 165:14
failed 165:8 215:18 217:5
failure 165:25 166:21
fair 15:13 24:1 44:1,24 117:17 118:7 164:23 181:21 184:7,8
Falconer 21:2 24:12,13 27:22 29:14,25 50:2 51:4,9,19 52:19 54:5 55:2,25 56:3 59:4,10,22 60:12 176:1 195:8,17,21,24 196:2,9,15 208:7,20 222:14,15 286:23 288:1 288:16 289:9 289:22 290:4 290:13,16 294:3,4,8 296:22 297:25 298:1 301:3,6 423:15 427:17 428:16,22 434:18 442:17 443:15,18,25 444:3
Falconer's 25:12 26:3,17 27:4,9 28:9,11 30:8 52:7,15 56:11 58:12 59:9,12 62:21 288:11 290:20 291:4 428:2 429:12 435:11,21 437:1,15 438:12 439:18 440:3,9,24 441:8 442:15
fall 76:25 146:25 280:3 321:5 322:17 323:7 330:2 340:19
fallen 241:13
false 42:20
familiar 74:10 142:17 181:12 183:23 227:16 238:18 241:11 276:5 294:11 294:15 368:12 368:18 381:11 381:12,15 386:20,23 387:1 391:1 396:7 405:19 406:4 410:21 411:2
familiarity 197:24 249:11
familiarization 125:17
familiarize 34:6 305:1
family 163:13
famous 112:6,7
far 205:4
faricimab 187:4 187:8,18 188:3 188:8 427:5 432:12
farsighted 103:13
fast 191:10
faster 100:4
father 206:19
fault 171:20
FDA 167:2 241:8 250:4 253:8 264:24 267:20 299:20 381:13 410:11 411:1
FDA-approved 153:9 178:17 179:16 188:1 255:7 257:1,12
FDA-recomm... 189:11
fear 318:5
fears 152:7,9
feasible 190:21
feature 157:18 373:14
feel 125:5 153:25 317:10 317:10 355:2
fellow 67:3 76:7
fellowship 65:12 65:18,19,23 66:21 67:9 68:9
felt 361:22
fewer 69:17,21 264:16 266:19 273:25 275:1 398:18
fiction 169:19
field 16:13 20:15 35:23 139:17 186:2 197:17 198:2 202:25 216:22 377:11 393:17
Fielder 429:23
Fielder's 430:16
Fifteen 80:4
figure 35:11 53:12 84:2 88:11 95:16 157:2 241:21 284:25 296:1,4 315:11 334:4
figuring 282:4
film 120:15 122:22
filter 173:5 177:18
filtered 179:12 179:15 180:14 181:7 184:14
final 56:6,12,17 59:12 62:20 273:8 277:15 435:22 436:8 437:5 441:14 442:1
financially 461:19
find 15:2 24:22 106:9 153:24 195:3 196:22 212:2 223:8 235:10 239:8 243:7 245:16 249:15 270:1 316:20 335:8 352:17 372:22 389:10 419:16 437:23
finding 87:18 332:22 405:16
findings 106:9 134:8
fine 42:22 407:4
finer 298:12,17
finish 25:23
firm 18:11 195:1
first 10:25 11:13 11:25 12:4,5,6 14:2 25:24 34:1,9 48:8 101:24 130:25 134:1,3 188:6 199:23 234:18 235:22 238:5 239:11 248:18 273:21 278:24 292:4 303:15 303:15 311:23 337:19 338:16 361:15 369:18 395:11 396:1 400:14 419:12 449:2
Fish 1:16 2:6 3:4 10:8 17:9,12 17:14,18 18:2 18:7,15 21:4 22:12 23:6 25:9 29:18 30:2 437:21 438:10,20
five 152:12

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 483 of 524

163:11 292:22 446:16
five-week 161:9
five-year 156:22
fixed 70:19
flip 211:20 249:5 272:11 449:11 450:15
flipping 233:4 233:24
floor 296:14
floors 295:17
flow 98:19 412:23
fluid 98:20 191:11 384:6
fly 316:23
focused 259:22 335:12
Foley 1:22 2:9 10:12 461:1
follow 189:10 279:15 314:14 322:24 323:2 326:25 360:1
follow-up 143:12 152:11 454:20
followed 133:25 134:6 175:14 273:14 279:12 280:18 407:24 408:3
following 50:5 65:16 101:21 150:6 348:25
follows 11:3
fora 157:7
forbidden 462:21
force 421:11,18 422:18 424:3
foregoing 42:14 461:9 463:11
forever 234:14
forget 238:4
forgive 147:22 216:22 229:18 350:13
forgotten 164:17 164:18 247:3
form 29:8 30:20 50:23 56:7,18 263:17 342:25 435:22 436:7 439:17
formal 194:3
format 157:21
formats 157:25
formatted 348:24
formed 205:1
former 16:11
formidable 257:11
forming 50:5,15 116:6 185:20 186:13 201:10 208:8 209:10 211:9 218:10 237:2,16 240:20 241:16 244:2,6 254:13 258:18 290:7,8 318:8 344:7 360:12 381:8 382:13 413:23 417:20 452:1
forms 70:13 435:24 436:2
formulate 255:23 361:23 364:2
formulated 100:5 303:19 356:21,23 357:1 360:3 366:25 424:22
formulating 119:9 195:10 224:24 256:11 426:3 454:4 456:10
formulation 19:24 21:2 24:14 58:9 141:13 171:21 171:23 172:22 173:4,10,14 174:14,18 175:2 176:2,6 182:10 191:1 192:15,20 193:1,21 194:7 195:11 196:19 215:12 221:12 221:17 224:5 236:13 249:18 252:2,4,7 255:3 286:6,16 296:6 298:2,11 298:14 299:25 300:21,24 301:15 303:7,9 304:16 312:10 316:23 319:23 321:12 322:2 328:19 332:13 334:10 342:13 342:17 344:14 349:14 350:19 352:25 354:25 356:15,17 358:3,18 359:7 359:20 360:3 363:16,23,25 365:5 367:13 367:22 368:1 402:1,7 421:6 421:10 425:2 425:22 426:25 427:10,24 428:4 445:17 451:2
formulations 38:9,16 219:24 293:18,24 304:12 328:9 335:25 336:14 336:14 342:22 345:7,7 352:15 359:19 360:14 361:2 363:17 366:7,8 419:25 420:7 424:12 424:14 425:4 427:4 428:18 429:3 457:7
formulator 199:17 201:12 201:17,20,22 202:3 204:24 204:25 221:18 295:9 296:5 356:5,14
formulators 356:9
Forster 113:15 114:23
forth 198:22 199:1,22 200:12,25 201:8 202:12 211:20 215:24 233:4,25 289:3 412:23 461:12
forward 439:14 449:11 456:15 462:12
found 105:15,18 196:8 223:8 368:15,18
foundation 126:21 131:21
four 65:22 71:4 92:4,5 114:8 133:17 152:12 163:11 211:13 212:25 213:2 217:16 260:4 260:12 261:18 276:11,14 277:21 281:5 281:14 326:13 379:22 391:7 392:2 401:23 404:7 409:18 412:24
four- 161:8
fourth 82:11
fractions 225:3
fragment 243:18 243:23
frame 266:1
frames 22:22
free 125:5 460:5
freeform 253:7
freeze 295:17
frequency 145:23,25 171:5 328:23 376:14 378:13 387:13 393:18
frequent 147:1 162:5 388:2
frequently 47:16 118:15 144:6,7 144:9 145:2,4 146:21 162:17 168:20
fresh 151:13
front 39:17 98:16,18 154:15 196:7 247:20 249:1 275:19 401:17 402:2 447:20
full 28:12 195:1 199:23 272:2 336:24 381:19
full-length 250:16
fully 76:8 144:16 181:19 220:7 332:10
function 93:19 102:11 122:22 228:20
functional 232:14

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 484 of 524

functions 229:15 230:21,23 231:2,21,23
fund 20:14
fundoscopy 111:5
fundus 110:14 120:11
further 41:2 42:18 77:18 155:24 222:20 430:25 446:11 457:23 458:1 461:9,14
fuse 226:20
fusion 36:7 38:11 198:6 203:4 226:21

G

G 412:5
gains 274:1 379:21
gallon 192:10
gate 279:11
Gaudreault 385:16,18 386:3
gel 97:10
Genentech 164:11 167:10 171:15 395:9
general 20:14 33:8 36:14 66:3,25 94:19 117:3 131:12 150:14 190:1,6 191:19 222:17 242:12 300:19 387:3 408:1
generalizability 425:2 429:2
generalize 123:17
generally 29:24 81:3 87:4 101:20 114:3 161:15 219:21 228:6 285:24 286:10 325:3 328:5 362:7 400:1,6 402:21 404:17,21 405:2,4,9,17 405:24 406:21 406:25 407:4 408:15 456:4
genetic 148:13 148:16,21
gentamicin 113:19,21 114:16
genuinely 271:22
germane 269:14 269:17 270:16
getting 45:17 89:21 90:4 121:6
give 10:18 19:15 23:22 91:22 101:6 112:1 130:22 131:2 141:5,7,22 142:6 144:22 145:5,24 152:19 161:2 177:25 187:18 215:2 218:12 220:25 225:9 253:13 267:22 292:10 300:7 305:1,5 310:4 317:14 332:13 334:9 367:20 376:21 377:1 446:16 451:1
given 24:20 114:5 139:24 140:8 145:25 146:20 147:15 148:1,2 149:2 159:13 173:13 225:14,15 252:15 256:2 265:3 273:15 279:25 280:19 282:10 283:16 342:22,23 404:7 410:7 423:2 463:15 463:20
gives 153:25 180:16 330:13 340:18 363:25 364:3
giving 115:6 153:12 169:1 295:18 418:24
glad 229:19
glaucoma 98:20
GLP-1s 162:20 167:25 169:25
glycoside 80:12
GMP 257:8 264:24
GMP-approved 257:13
go 35:10 45:1 46:9 51:20 66:9 77:1,2,2 84:12 90:18 95:15 117:13 119:15 121:23 130:12,15 133:12 135:21 147:2,3 150:18 152:6 153:22 155:10,12,15 155:17 159:18 160:8 163:10 166:15 170:5 174:10 176:5 178:3 179:16 187:17,21 197:12 207:7 210:21 220:19 221:5 231:12 233:4 243:12 256:23 273:12 275:10 284:11 295:21 302:7 302:10 303:13 304:22 305:13 306:10 310:5,8 322:7 323:1 325:13 334:15 346:12 356:24 367:19,21 381:7 382:19 386:2 390:5 398:21 400:13 403:17 410:13 416:20 418:15 434:17 444:21 446:18 448:4 449:8 454:25 455:4 456:14 456:17
goal 98:7 165:3 166:5 365:4,8 365:12,14 375:15
goes 14:7 92:11 92:16 113:13 134:2 185:4 216:3 247:22 277:19 280:16 280:16 340:14 358:17,21 373:22 422:16
going 14:25 15:2 15:9 29:21 30:1 31:8 40:3 41:1,6 46:4 58:16 61:14 62:23 65:9 79:7 83:10 95:3,8,14,19 115:22 118:3 124:20 131:1,2 139:24 140:1 146:4,21 149:21 151:10 155:5 156:7 160:22,24 161:18 163:5 223:15 233:14 233:18,18,25 239:23 247:5 253:12 261:24 264:23 265:10 276:17 279:20 280:25 289:3 289:16,23 295:16 298:11 313:5 322:7 355:22 373:17 376:22 378:19 384:1 387:6 399:6 422:25 447:7 448:5 449:8 454:25 456:13
goldilocks 328:17
good 9:18 11:6,7 136:24 150:9 162:18,23 220:8 225:25 230:2 294:25 296:12,15
Google 369:10
governing 462:14
governmental 326:24
gradation 298:17
gradations 298:9,13
graded 297:17
graduate 65:1
Graefe's 6:13 106:19
gram-negative 80:20
grandfather 261:10
grandfather's 73:15

gratia 454:12
great 14:6 158:21 411:23 446:20
greater 73:19 241:19 264:20 383:7 384:15 385:25 394:6 394:15 396:11 396:21 398:5 416:4 429:8
greatest 332:14 334:10
Greek 430:6,11
green 215:7 426:16
grew 75:20
ground 13:25 48:25 49:3,7 49:16 218:21 219:3 220:3 305:9 450:6,9 450:10,21
Ground4 49:11
grounds 449:24 450:2,17
group 1:23 9:9 103:25 252:22 264:16 266:19 339:9 395:1 462:19,20 463:1
grouped 339:14
grouping 255:17
groups 135:25 392:3
grown 69:10
growth 227:19 227:23 228:23 230:4,9,13,18 230:19 231:8 231:24 232:15 232:18 233:7 233:20
guess 102:16 106:7 162:12 251:4 259:21 366:4 398:1 416:14 451:10
guest 10:3 46:3
guidance 80:9
guide 36:4,12 45:22 116:19
guided 335:7 367:10 445:16
guidelines 183:7

H

H 6:2 7:2
habit 194:22 426:9
hair 215:7
half 114:7 385:22
half-inch 423:1
half-life 113:18 114:1,3,4,9,14 114:19,24 115:5,12,14,20 116:5,14 117:16,20 118:16 119:3 235:1,14 236:4 242:17,23 244:1 251:8,16 251:18
hand 10:15 31:8 40:5 76:24 79:7,16 95:20 124:20 195:15 255:14 276:1 299:9 456:10
handle 40:2
handy 310:1
happen 258:23 268:23
happened 37:16 53:2,3,5 135:22 257:19 408:23 410:17 433:20
happening 433:19,22
happens 183:24 184:17 217:25 233:6,8
happy 57:13 102:7 235:9 236:1 272:1 276:21 303:17 317:16,22 360:7
harass 46:4
harassing 45:17
Harbor 244:18 244:23 245:4 245:14,23 246:1,1,16 261:15 265:2 266:4 267:1 283:3 284:21 326:14 377:17 380:7 382:20 391:24 392:1 394:13,13 396:4,5 397:9 397:24 412:23 413:18
hard 95:15 132:12 423:20 438:25 439:17
harm 92:18 108:16
harmful 180:19 186:4 242:10 383:25 407:7
Harvard 66:11 68:15,18
HD 188:3
head 223:12 251:11 313:25
heading 400:15 455:16,18,25 456:1
hear 149:17 150:3 235:12 342:12
heard 301:23 327:6 434:5
heart 63:18
height 102:21
held 188:21
help 68:7 69:2 79:10 86:7 197:1 201:14 235:7 289:11 297:21
helpful 92:24 128:25 221:12 284:17
hereinbefore 461:12
hesitate 462:16
Hey 253:11 266:21
HF 1:4
Hi 206:13,14
high 103:16 191:4 236:15 236:20 237:5,8 267:12 294:24 294:25 296:18 299:24 325:6,7 325:11,11 334:17 335:16 355:24 356:22 356:23 388:21 393:14 401:13 407:9,12 416:18,21 417:5 445:5 456:11
high-risk 136:21
higher 19:24 100:6 101:7,7 134:23 141:25 187:7 220:19 224:5,8 225:5 240:16 241:5 242:11 249:17 253:24 263:15 264:6,19,25 265:14 266:4 268:5 269:4 270:11,20 278:15 285:8 286:3 297:10 302:6,9,13 313:4 334:25 366:16 367:19 367:20 376:21 377:8,11,12 384:1 386:16 388:18 395:2 398:20 418:19
highest 267:23 301:13,14,24 332:12 334:8 335:17 415:12
Highlights 7:5 247:8,21
highly 83:21 116:12 131:4 186:4 188:12 224:4 225:4,8 234:21 243:23 396:23 410:24 422:20 423:8
hinges 338:11
Ho 245:16,16 246:4,15 391:17,25
Ho's 245:2 246:7 246:19,21
hold 68:25 117:9 234:12,13 376:24 378:21 424:1 449:10 449:10 454:24
holding 421:25
home 169:2,15
honest 310:3
honestly 110:17
hope 272:25
hopefully 108:21
Hopkins 12:17 16:10
horizon 144:19
host 154:10 175:9 453:20
hot 105:11

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085

hour 95:3
hours 16:22 22:16,19 23:20 26:4 113:18,21 113:22 114:8,9 114:17,17 278:23 292:14 292:22,22 446:7
Hufnal 434:13 434:15
human 86:20 101:1 228:16 231:22 267:18 385:4
humanized 243:17 250:17
humans 101:17 102:15 103:9 104:11,20
humor 96:25 97:22 98:20
hunch 399:5,6
hundred 140:1 179:1 309:12 315:13,16,19 316:7 318:18 318:25 320:12 321:20 323:10 328:1 331:24 331:25 335:3 338:10,10 345:9 362:21 401:22
hundreds 284:22,22,23
hurry 125:10 138:15
hypothetical 68:1 137:18 140:24 145:16 157:12 170:18 172:2,25 181:1 417:23,25
Hyung 107:2

I

ice 278:20,21,22
idea 182:25 183:4 193:15 194:15,19 304:2,10 356:11,12 408:9 409:2,8 427:21
ideal 299:15
identification 79:14 95:25 106:21 124:25 247:10
identify 9:16 47:24 411:14
IgG1 243:17
ignorance 65:10
ignored 403:22
ignoring 141:2
ii 276:19 277:6 277:10 448:14
iii 448:15
Illinois 64:6
imagine 104:3 169:22
immediately 64:23 65:15,15 213:21,24 409:20 416:10
immense 37:8
immunosuppr... 136:22
impacts 217:1,6
impetus 321:23 324:22 327:16
implied 389:20
implies 154:4 397:3
imply 111:9 141:21 397:2
important 14:11 114:19 116:22 117:5 118:16 118:22,23 119:1,3,5 156:11 158:5 180:9 185:13 208:1 242:3 249:1 261:21 282:4 290:5 303:21,22 373:13 383:19 383:22 413:24 414:6 423:8 441:23 442:3
impossibility 299:10
impossible 420:24
imprecise 315:22
impression 174:13
imprisonment 42:22
improper 255:5
improve 164:3 171:10 261:13 261:19
improved 262:3 266:6
improvement 163:14,20,22 278:1
improvements 392:4
improving 384:7
impure 183:25 184:3
impurities 183:2
impute 406:3
imputed 201:11
imputing 282:22
in-house 4:3 10:1
inaccurate 162:11 300:2 318:5 390:1
inactivate 238:25
inactive 172:21
inaudible 394:8
inbox 437:24 438:9
incapable 338:12 418:24
inception 171:9
incidence 136:2
incidences 136:10
incident 138:8
incidents 393:24
inclined 254:11 326:25
include 22:3 151:18 154:7 159:4,10,12,15 345:2,11 348:6 348:7,8 355:3 359:19,20 457:4
included 156:16 197:16
includes 200:18 426:22
including 57:10 175:16 197:18 197:20 198:6 203:3 347:21 462:21
inclusions 87:16
inclusive 407:6
incomplete 137:17 140:24 141:12 142:8 143:19 145:16 170:17 172:1 172:25 180:25
incorporate 138:5 228:9
incorporates 427:6
incorrect 166:1 223:24
increase 242:2 254:16,22 260:11 263:3,5 268:4,23 280:12 282:6 283:24 284:3,6
increased 258:21 260:9 394:5,14 396:10 409:21 413:1
increases 191:3 258:1 274:22
increasing 241:18 242:1 253:19 254:15 254:21 257:23 258:1,20 260:8 260:10 261:18 262:10,14 268:3,17,20 274:22 280:11 281:1 282:5 284:2,5 371:12 372:19 373:9 374:4 375:1 376:12 378:10 380:1 383:6 384:13 385:24 387:10,24 388:8,13,24 393:19 412:22 418:9,11 424:3 424:3
incredibly 173:8
independent 451:22
indeterminate 59:16 60:5,13
INDEX 5:2,5 8:1
indicate 152:10 211:4 214:14 215:10 448:18
indicated 57:11 219:19 224:11 248:19 361:18 362:11
indicates 74:13 81:17 129:8

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 487 of 524

205:22 219:24 405:23
indicating 91:20 135:4
indication 89:19 90:1,8 94:14 264:3,25 266:8
indications 250:2
indicative 386:11
individual 82:13 82:16 85:3 199:3 205:20 206:1 451:21
individuals 150:1 198:8 203:23
indocyanine 426:16
infected 421:16
infection 72:9 108:14 135:16 161:6 184:9
infections 80:22 136:22 184:21
infer 81:24 91:6 257:19 406:3 409:19
inference 92:9
inferences 258:13
inferred 92:21
inflammation 72:12 165:20 166:14 188:15
influence 362:17
inform 418:2 454:14
information 7:6 21:5 25:6 29:13,16,23 34:25 35:22 36:14,20 42:17 56:7 59:9,17 61:2,11 91:7 94:2,20 134:10 136:15 138:20 141:12 150:25 153:25 155:11 155:23 159:12 160:11 175:9 179:13 183:21 189:6 194:1 217:21,23 218:1,3,4 221:10,10 223:17 236:3 237:13 242:4 242:12 247:8 247:22 249:1 254:24 257:11 257:21,25 258:10 278:14 280:5,9,10 281:25 282:3 287:17,22 301:7 320:2 321:18 322:4 325:1,7 383:22 401:8 403:8,11 403:18 404:12 404:15 409:25 410:21 411:5 418:1,22 419:1 419:4 424:7 440:17 459:1
informational 154:11
informative 116:9 270:11 282:10 283:17
informed 210:23 296:22 442:19 443:4 448:11
informs 258:22 259:9
infusion 424:17
ingredients 172:20,21 174:18,20 175:11,23 176:5 215:6 427:18
inherently 157:22
inhibit 229:4
inhibits 228:25 230:19 231:6
initial 97:17 125:16 249:10 269:18 297:20 299:16 321:23 326:20 327:16 404:8 451:5
initially 252:22 281:13 301:6 341:19
initiate 152:1
inject 70:20 71:20,22 97:16 115:19 144:12 145:1 168:9 178:21 182:9,9 183:25 186:18 188:9 190:10 190:12,15,20 220:25 238:15 294:22 296:9 302:15
injectable 169:14 222:7 300:20 332:16 451:4
injectate 191:3 287:2 295:2 364:8 421:3
injected 72:11 98:22 99:5,9 100:18 106:5 107:23 108:4,6 128:23 146:22 162:16 169:25 170:12,14 171:22,23 173:16 184:14 184:20 191:20 260:19 357:4 401:11
injecting 100:23 101:15 102:12 128:17 162:20 180:22 181:3 181:24 188:23 252:17 420:18 426:10,14
injection 38:22 107:13,14,24 108:17 109:15 109:25 110:6 110:11,22 111:21 116:7 120:13 132:9 145:22 147:4 152:8,12,19,20 152:22 161:5 163:9 169:1 170:23,24 171:4 174:21 176:10 184:11 189:16,16,20 190:2 191:15 191:18 193:12 194:17 197:20 222:8 239:1,12 252:5,8 261:7 271:2 273:22 298:4 299:1,4 307:20 318:17 318:19 319:1 322:22 328:22 354:20 357:8 357:11,17 358:3 359:10 361:24 364:19 366:9 367:18 370:16 371:1 384:22 385:6 401:5,6 409:12 423:2 424:16 426:21 429:6 429:24 430:17 430:18 431:2 431:24 432:8 443:19 444:4 444:19 445:4 457:12
injections 71:2,9 76:25 77:5 78:19 107:16 107:19,25 111:23 113:11 117:19 118:11 139:5 144:6 145:14,18,19 145:24 146:5 160:25 161:3,8 168:11 170:5 185:2 262:1 264:16 266:19 270:19 271:6 273:6,15,20,25 274:7 275:1 277:12,21 280:20 282:15 376:15 378:13 387:13 388:3 393:23 395:2 398:19 426:11 431:1
injector 366:16
ink 41:15
inner 88:20
inorganic 426:13 427:8 427:22
inputs 154:16
inquired 17:4
inquiry 34:10,11 454:21
ins 386:21
inside 47:2 98:17
instance 83:24 90:25 111:20 138:24 141:23 232:16 233:5 282:21 318:17 370:14 413:17 437:21

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 488 of 524

instances 188:14 325:24 326:4 404:17
Institute 67:4
instruct 29:21 30:1 289:17,23
instruction 13:23 34:4 403:13
instructions 152:24 179:17
insulin 170:25
insurance 186:21 187:11 187:12
intended 458:15
intention 88:24
interaction 88:2 410:25
interest 189:4
interested 164:2 225:9 254:12 255:1 330:22 362:9 393:17 461:19
interesting 319:17
interleaf 162:2
internal 361:3
internet 16:3
internist 168:6
internship 64:22 65:6,11,13 66:1,4
interval 116:8 116:23,24
intervals 119:10 134:5,7 145:20 162:5 299:5 399:20
intervention 123:13
intimately 396:6
intra 129:3
intracameral 74:16 126:18 128:17,23 129:6,11 131:3 131:9 137:12 139:5 140:9 141:24
intracamerally 131:18
intramuscular 183:20 424:16 429:6
intraocular 72:9 80:22 129:4 191:4,13 243:19 366:2 374:17 401:14 409:21 421:4
intraocularly 426:14
intravenous 183:20 248:15 424:17
intravenously 429:4
intravitreal 72:13 74:15 80:12 96:12,22 102:19 103:10 107:3 110:4,7 111:21,25 113:11,18,20 114:16 118:8 118:10,15 120:13 127:17 129:9 130:20 131:3 144:5,14 145:14 149:15 149:17,22 172:23 175:24 183:9,17 185:1 190:8 193:12 193:20 194:16 195:11 196:19 197:20 222:8 239:1,3,12 252:5,8 258:2 357:8,11,16,21 358:3,15 359:9 363:17 364:6 367:1,17 384:21 385:5 393:23 425:21 426:11,21 427:18 428:4 428:19 431:1,2 431:13 443:2
intravitreally 78:4 164:5 171:24 260:1
intravitreous 248:16
introduced 264:13
invalid 32:25 33:25 34:21
invalidate 210:11,18 217:22
invalidation 217:22
invention 197:14 215:19 216:25 217:6
inventors 237:14 237:21
investigating 393:18
investigator 132:1 154:23 238:10 408:19 410:4
investigator's 158:12 244:25 382:14 390:16
investigator-i... 283:8
investigator-s... 283:18
investigators 156:3 279:6 391:24 405:1
involved 17:2,16 23:14 69:23 77:25 98:4 255:19 369:3
involves 35:6 289:21
iris 98:16
irrelevant 118:1 180:9
irrespective 55:15 266:11 347:9
irritating 92:10
isoforms 227:13 229:1,5 230:13 230:17
isolated 138:7 141:23 142:7 143:18 188:14 224:13 325:2 325:23 326:3 374:13 399:22 399:24 400:5 401:3 402:9,24
isotype 243:18
issue 17:6 30:23 69:22 180:12 216:4 256:12 270:16
issues 11:22 16:20 36:25 137:24 152:21 222:16 286:24 287:2 376:10 401:15
Italian 158:21
item 216:18 306:7 337:25 338:17 339:11 340:4 341:11 341:18,18,21 341:23,25 342:9 362:12 363:7 369:20
items 37:23
iv 448:17

J

J 1:14 2:5 5:6 10:24 54:5 461:6 462:2 463:8 464:4,25
job 35:10 296:1 296:4 367:22
John 12:16
Johns 16:10
Jonathan 4:9 9:7
Journal 6:6,10 6:19 79:12 95:23 124:24
joy 163:1,12
Juarez 4:9 9:7
judge 14:16
jump 326:12,19
June 1:20 9:9 50:3 51:7 52:2 53:4 60:7,16 291:12 461:25
jury 434:5
jux 346:13

K

Kane 23:11
kappa 243:18
Kat 11:9
Kathryn 3:16 9:19
Kayali 3:16 5:7 5:9 9:18,19 11:5,9 26:24 27:1,13 29:1 30:4 31:3 40:11,13 45:15 45:21 46:10 54:3 79:8,15 79:20 81:12 90:2 93:2 95:7 95:12 96:2 103:24 106:15 106:23 109:17 110:1,5 114:20 114:22 120:1 123:21 124:2,5 124:13,15,20 125:2 126:3

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 489 of 524

131:22 140:18 148:19 170:9 170:11 182:12 202:1 207:12 207:18,21,25 208:5 209:15 209:17 221:4 225:23 226:4 226:15,16 238:1 247:5,11 247:16 253:20 255:11 257:20 257:24 277:24 290:1 291:21 293:1 306:9,22 310:9,12 317:25 331:15 349:3 372:6,11 372:13,15 386:7 387:5 390:20 391:20 391:22 411:19 412:11 414:23 415:22,24 432:17 444:9 444:15 446:8 446:17,20 451:13 452:21 458:2 460:4
keep 95:8 142:13 154:17 168:11 192:15 192:20 193:1 372:9
Keeping 101:11
key 36:24 266:17
keyed 302:19 365:1
kidneys 97:24
kills 126:13
kilogram 149:3
kind 15:4 22:19 59:1 121:6 126:4 138:19 165:24 184:12 187:9 211:16 252:25 286:5,6 286:15,16 301:2 333:22 361:14
kinds 70:11 176:23
kinetics 234:13
kitchen 153:12 153:18
kkayali@wc.c... 3:22
knew 37:21 39:7 55:18 57:1 220:20,21,23 363:21
know 14:5 15:6 16:6 18:20 22:4 27:22 31:19,22 33:16 36:5 53:4 54:23 56:17 63:16,18 67:23 73:15 75:19,24 77:16 82:8 84:10 92:19,19 94:23 95:4 97:4 99:24,24 102:3 119:5 122:19 125:7 126:5,13,23,25 130:13 133:16 137:19,21 138:1,2 141:8 149:9,21 150:22 151:24 152:3 154:5 157:4 158:19 163:7 164:22 166:11,17 167:5 172:10 173:10 179:1 179:21 181:2 182:24 187:19 188:20 195:5 195:22 206:23 208:7,25 213:13 214:20 214:24 215:13 216:24 217:16 221:20 223:14 228:21 233:13 234:3,13 236:19 239:21 239:21 248:17 250:23 251:10 253:18,22 257:8,15 263:17 265:21 265:21 269:2 271:23 275:13 275:15 278:25 279:25 282:12 282:13 283:14 283:21,24 284:2,19 290:6 290:8,11 292:11 295:5 295:15,18 297:3 298:19 299:21 312:22 312:23 315:23 317:5 326:14 346:17 351:9 356:8,21 360:18,23 381:22 382:1 385:22 395:21 401:2,10,14,20 401:22 402:6 402:10 403:3 406:5,9,12,14 407:17,23 408:6,11,23,24 409:4,10,14 411:4,8 414:11 422:19 423:25 433:19 434:8 434:12 436:10 436:17,21 438:15 442:14 442:16,22,23 448:7 453:25 455:8 456:23 459:2
knowing 56:12 175:10 427:4
knowledge 17:15 18:3 20:14 24:10 37:9 42:16,20 50:16,18 56:23 76:14 89:22 116:13,14 132:10 139:14 179:18 186:15 194:25 197:17 215:22 240:23 267:16 271:19 328:22 381:5 418:9 426:24 427:3 434:6
known 29:9 112:14 123:15 184:25 243:21 410:15 441:24 442:12
knows 191:18
Kristi 23:12
Kwak 107:2

L

L 229:21
L.L.C 463:1
lab 166:15 423:6
label 218:24 219:6,11,18 224:11 252:10 261:8 294:2,12 311:25 324:17 324:23 325:1 325:23 326:24 327:10,17 328:7 332:10 332:25,25 333:18 354:15 362:11 365:4 369:16 374:12 399:1,12,24 400:19 410:23 411:6,15 430:19 450:11 456:7
labels 411:11
Labs 12:17
lack 112:21 178:13 433:15 433:15,25
lacked 434:4
laid 342:4
lamellar 87:16
lane 79:24
language 46:24 339:21 340:1,2 341:8 346:23 347:2 352:2 353:25 354:8 397:19
large 135:25 157:18
large-scale 175:15
largely 29:9
larger 364:15 421:10,15
Larson 219:6,12 219:22 221:19 221:21,24 294:2,12 296:17 324:5 328:14 365:4 419:21 420:3,6 424:10 425:12 427:20 428:3 428:17,25 450:12 454:21 456:7 457:6,17 457:20
lasted 271:13
late 46:17
lately 168:1
latitude 364:1,3
law 34:7 410:22 411:2
laws 42:12

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 490 of 524

lawyer 10:5 11:9 17:9 313:1 315:21
lawyers 14:18 55:7 57:10,18 59:11,23 290:20 291:3
laxity 135:4
lead 105:11 346:18 388:1
leading 451:13 452:21
leads 262:10
leak 178:24 421:16
leakage 165:15 232:24
learn 94:7
leave 68:21 421:15 445:18
leaves 98:20
leaving 355:8
led 261:15 293:22 401:3
leeway 332:14 334:10
left 114:7 216:22 419:22 444:12 445:9
left-hand 31:13
legal 9:8 34:10 35:15 36:10 39:11 75:14 120:23 121:17 122:15 123:8 133:11 134:17 197:5,5 199:19 202:7,10,21 204:11 205:16 205:25 206:3 209:20 211:8 217:8 262:21 307:3 337:17 338:11 346:5 433:24 447:9 448:1
legalism 223:6 223:25
Legally 39:25
length 422:24
lengthy 72:2 86:16 148:24 149:11 292:9 292:11 424:17 433:4
lens 73:11 96:24 97:8,12 100:11 103:5 109:10 265:8
lesion 230:24 232:20
lesions 165:16 165:24
let's 14:3 24:23 30:6 33:22 38:2 79:6 95:10,18 102:16 109:2 123:21 137:5 145:8,9,11 151:12,12,13 151:24 172:18 176:10 184:11 190:8 197:11 198:18 201:20 207:20 212:2 218:11 219:13 226:2,17 229:24 235:4 236:21 243:12 248:5 249:3 255:16 259:8 275:2 304:22 313:17,17 315:3,24 317:25 324:7,8 349:4 368:4 370:4 372:6 379:15 390:10 390:21 397:11 398:21 410:4 411:17,19 419:8 434:17 434:17 447:19 450:1 453:15 455:3
level 14:25 83:14 84:11 89:6 92:15 115:22 133:20 134:23 191:6 211:1 212:7 232:14 267:23 326:9 407:10,12 448:14
levels 84:2 87:2
liberty 59:5,8
licensed 204:13
lid 122:22 136:22
lifts 154:9
light 88:10 217:21
limit 89:22 208:14 297:13 355:7,11,13,15 355:18,19 422:11
limitation 77:4 279:2
limitations 86:3
limited 91:14 111:15 169:23 307:20 345:12 453:13
limiting 162:9 322:10 396:23 421:20
limits 194:24 417:11
linchpin 376:20
line 8:4,9,14,19 82:12 189:22 362:4 430:9 464:8,10,12,14 464:16,18,20 464:22
linear 422:19 424:4
lines 13:13 25:7
liquid 174:15 177:22 178:11 179:5,7 296:13 335:25 336:14 345:7 349:13 350:18 419:25 420:25 422:23 423:9 424:12 425:3 429:3
list 119:4 149:11 174:17 193:25 272:12
listed 50:23,24 54:7,9 291:11 326:24 351:13
listen 160:7
lists 50:13
literal 88:25
literature 20:12 21:7 112:12 183:24 184:16 185:7,19 186:12 239:13 240:19 251:5 386:18 403:20
little 40:21 57:15 73:24 107:13 233:10 241:1 255:20 298:8 435:18 446:14 448:13
liver 97:24
LLP 3:15
loaded 257:6
loading 274:5 282:17
loads 172:11 187:20
local 410:12
located 47:2 406:10
logarithmic 424:5
logical 326:16 404:6,9
long 14:4 19:1,7 22:15 99:18 151:23 266:18 275:9 292:7,17 294:11 391:23 407:24 408:3 410:18 439:11
long-term 94:2
longer 167:6 187:6,12 241:19 253:25 262:11,15 263:7 265:5 266:10 271:13 274:24,25 278:16 279:13 376:23 377:10 377:12
longer-lasting 165:4 166:6 167:12,15
look 32:2 79:6 85:16 87:7,10 89:8 95:18 107:5 113:7 123:22 153:23 155:18 157:13 159:18 174:14 178:12 210:2 241:3 248:25 249:7 252:24 266:8 271:20 275:13 303:17 304:23 334:13 341:18 359:24 368:4 376:8 380:22 381:7 385:8 390:21 391:9 393:11 397:11 399:2 411:10,17 419:8 424:10 431:20 435:1 435:15 447:23 447:24 448:6

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 491 of 524

450:3 451:17 452:11 453:15 456:22
looked 28:8 33:3 80:2,11 95:17 107:25 110:7 111:4 173:13 173:18 212:9 224:8 239:8,13 266:20 269:19 275:4 276:9 285:15 286:1,4 286:14 324:10 328:8,8,14 354:16 365:15 365:16 391:5 417:5,8 436:18 436:19 437:25
looking 33:4 40:4 92:13 93:3 111:5,6 153:18,19 166:19 167:21 173:25 174:1 174:15 177:6 178:9,10,19 212:18 219:2 245:4 248:22 261:16 269:23 279:7 283:12 284:5,7 298:6 298:25 313:23 320:4 326:17 330:6 332:9,12 334:8 371:7 373:1,4 383:3 386:15 387:8 404:10,11 413:8 430:9,13 436:15,21 447:15 448:2 450:20 452:1,3 452:6 455:17 455:20
lose 111:10 405:5
losing 188:23
loss 93:18
lost 87:9 245:21 314:24 340:9 353:16 376:24
lot 33:15 84:12 110:17 147:22 153:3 162:13 163:12 300:3
lotion 118:2 215:4
lots 121:8,10
Loure 80:9
low 103:14 189:3 190:20 236:16,22,24 263:17 296:19 300:19 395:22 412:22 424:11 424:11 425:2,3 429:2,2 444:20 445:4
lower 100:2 191:14,19,20 240:16 241:5 264:20 268:6 269:4 270:12 270:20 302:7 302:10,15 309:15,16 318:20 351:16 364:14 366:17 367:21
lowest 260:25
Lucentis 255:10 255:15 259:8 260:5 411:7
lucky 135:23
ludicrous 420:23
lunch 207:10,15 226:2 306:24
Luncheon 226:8
lysosomal 87:16 112:11

M

M 1:23 4:4 463:2
M.D 1:14 2:5 4:4 5:6 10:24 461:6 462:2 463:8 464:4,25
mac 78:1
Macugen 7:5 225:12,13,16 238:6,11,15,19 238:22,23 239:9,10,10,18 239:19 240:3 240:12,20,24 240:25 241:4 241:11,18,21 242:15,17,24 243:2,4,7 247:7,23 248:14 249:21 255:10,14,18 256:7 260:5,18 261:3,7 267:7 267:14 300:13 365:20 427:5
macular 17:6 20:1 33:8 36:15,16 58:7 77:8,23 78:1 147:12 165:16 165:24 230:24 248:20 249:21 249:22 279:23
Madam 14:1,8 79:10 208:2
mail 438:25
mailed 439:17
main 163:5
Maine 3:19
maintained 274:1 392:3
maintenance 232:9
major 159:12 164:24,25 186:3 241:22 440:15
majority 78:7 188:18
makable 221:17
making 75:17 108:21 135:5,5 213:6 223:3 319:3
malfunctioning 306:12
malpractice 11:22
man 460:6
manage 76:10 168:9
management 76:21
Manhattan 163:8
manifestations 87:14
manner 7:9 215:1
manufacture 198:4 203:2
manufacturer 164:24,25 166:4 178:25 179:13
manuscript 272:16
map 256:3
Marie 1:22 2:8 10:12 461:1
mark 95:13 247:5 372:6
marked 8:18 79:9,13,16 95:21,25 106:17,21 124:21,25 247:9 276:3 298:12,17,18 304:23 372:14 390:25
market 165:9 167:15 188:17
marketable 165:17,19,19
marketed 395:11
marketing 166:20 397:5
marking 189:22
Martina 434:13 434:14
masse 168:2
massive 326:9 374:17
material 34:14 92:22 250:21
materials 208:16 210:8 272:12 380:25 385:9 385:14 401:17
math 225:18,22 298:7,24 310:15 312:24 313:9 316:23 331:22 333:22 363:9
mathematical 315:23
mathematician 315:21
mathematics 307:16
matter 9:13 50:6 76:11 98:25 104:25 105:6,7 204:17 403:6 456:10 462:7
maximum 193:10 194:15 222:7
mean 12:7 20:19 33:16 40:7 43:8 44:16 67:23 76:18 82:25 85:21 93:12,23 96:17 97:5,15 109:21 111:17 122:2

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 492 of 524

131:18 144:10 145:17 147:21 158:15,19 162:19 170:19 173:1 182:15 192:9,10 200:11 205:10 214:18 221:7 223:2 230:25 231:5 234:18 275:11 279:12 281:6,8 286:21 287:10,25 295:13 298:16 325:19 337:14 345:21 357:7 373:21 375:16 385:3 387:20 387:21,22 396:25 404:22 458:21
meaning 396:11 440:9
meaningful 263:14 264:8 264:14,21 265:9,12,18,20 265:22 266:14 266:16 392:15 393:2 394:21 394:24 395:8 395:20 396:19 396:22,24 397:1,22
means 15:22 43:6,9 59:21 61:10,14 93:14 194:4 251:16 265:9 288:2 292:12 357:16 360:25 387:17 402:24
meant 247:2 387:23
measure 93:9
measured 102:21 104:22 422:21 457:15
measurements 422:23
measuring 94:11
mechanism 106:9
mechanisms 97:20
medical 11:22 16:20 22:4 58:5 64:4,8,10 64:16,18,19,21 64:23 65:1,7 65:16 66:4,11 67:12 76:10,12 76:17 77:1 78:4,10,17,18 78:22 79:2 136:15 142:10 143:17 197:16
medication 16:21 177:5,7 177:8 190:22 373:24 407:3
medications 149:6
medicine 66:15
Medicines 372:4
medium 100:22
meet 22:11 202:4 205:2 206:12 438:20
meeting 442:24
meetings 21:19 23:5,16 24:2 154:8 155:20 396:6
meets 190:25
Megan 3:5 10:7 23:11
member 238:12 288:5 403:7
members 23:6 288:8
membrane 94:24 426:17
memory 24:20 79:24 194:10 195:14 196:13 240:5 368:10 370:2
mental 158:20
mention 130:19 130:24 235:14 311:7 352:6 358:7,10 398:18
mentioned 52:25 60:4 70:10 97:11 102:9 127:2,4 128:3,11 148:21 167:10 177:13 185:12 187:6 235:21 235:25 242:20 250:2 255:22 370:10 388:6 421:23 433:2 442:20 457:9 457:11
mentions 70:16
mentor 206:18
mentoring 69:24 71:15
merely 120:10
Merit 2:9 461:1 461:23
meshwork 97:21 98:12,15
metabolisms 86:13
method 142:9 424:23
methods 164:3 222:22
metrics 145:6
mg 131:24 309:17 345:8,9
mgs 301:16 302:14 304:4 304:11,19 308:17,18,19 309:2,2,3 310:19,20,20 313:15,16,16 313:18,18,19 314:17,17,18 315:6,8,15 316:1,3,7 320:9,11,12,12 320:19,20,20 331:18,22 334:11,22 336:15,16 337:2,2,2,3,3,3 337:5,6,6,7,7,7 337:8,8,9 338:3,5,20 339:1,3,19,22 339:23 340:22 340:24 341:1 346:24,25 349:16,19 350:20,21,23 352:1,24 353:3 353:4 354:1,2 354:8,9 355:6 355:9,17,19,20 356:15,17 357:14,15 358:1 360:3 361:12 363:15 363:17 364:10 364:17 366:6 370:15 379:22 412:23
Miami 67:4
Michael 23:11 65:7 245:7,8,9 245:12
Michelin 158:23
microgram 220:22
micrographs 112:25
microliter 225:5 299:1 301:9 312:20 314:9 314:10 318:17 318:18,24 332:16 363:24 364:8
microliters 38:23 104:22 190:10,11,12 190:16,16,17 191:17 220:15 225:3,13,19,22 240:6 243:9 253:3 298:8,10 300:12,14 307:21 309:11 309:12,18 312:11,17 314:22 315:13 315:17,19 316:2,13,17,20 319:7,10,24 321:16 322:1 322:23 323:10 324:3 328:13 331:25 354:22 362:23 363:2,5 363:11,20,22 363:25 365:13 365:19,20 367:16 368:3 370:17 371:4 401:23,24 430:1,7,18 431:3,9 443:20 444:5 451:5
microns 102:22
microscopy 110:14
middle 44:17 366:18,19
midnight 43:18 43:23 44:2,7 44:15,19,22 45:1,4,10 46:12

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 493 of 524

miles 192:10
mill 103:21
milligram 89:9 91:11,13 92:15 103:2 114:5,7 126:23 127:12 127:24 133:3 137:14 140:14 141:14 149:3 219:19 220:14 220:22 224:12 225:1 248:14 261:3,3 264:10 269:19 271:11 271:12,13 274:12,14,21 274:23 277:14 277:14,15 278:9,9 281:4 281:21 286:12 294:6 296:23 297:5,9,15 298:5,6 306:3 312:7,9,14,16 319:25 320:4 321:24,25 324:12,15 325:24 326:15 327:9,23 328:4 329:6 330:22 331:1 332:9 333:13 360:9 360:20 363:6 368:3 369:5 370:6,11,25 392:13,17 393:1,4 394:20 395:6,11,15,15 396:18 397:21 400:19 401:5,6 402:7,10 403:9 403:12,19 404:13 405:17 405:23,25 406:20 407:20 407:25 408:8 409:16 414:8,9 416:22 451:2
milligram-per... 85:16
milligrams 36:5 38:4,10 39:3 83:9,10 132:3 133:3 134:11 134:12 137:13 137:20 139:6 140:16 141:17 219:16 220:20 224:16 236:25 237:11 240:10 241:5 243:8 249:25 252:23 253:3,6 265:6 266:24 273:7,8 277:13,13 281:13,20 285:14,17,23 286:9 293:19 294:19 297:1 297:10,12,14 298:22 300:24 301:7,8,19 302:12 305:25 307:17 308:5,6 308:7,21,22,23 310:22,22,23 311:3,8,20 313:24 314:13 314:17 316:19 318:21 319:18 320:5,15 321:6 321:14,14,15 321:20 322:18 323:8,12,19 325:12,14,22 326:4,6,14 327:20,22 328:10 329:20 330:3,12,15,16 330:21,23 331:8,9,10 332:1,6 333:1 333:6,24 335:9 335:10,11 336:2 338:24 349:16 354:16 354:17 356:1 357:8 362:1,10 362:22,25 363:3,8 364:7 365:8,14,17 367:11,12 368:16,22 369:10 371:13 372:20 373:10 373:16 374:5 374:13,16 375:2 379:20 394:3 399:15 399:20,25 400:6,9,18,23 401:4 402:3,20 403:24 404:9 404:17 408:25 409:6 415:13 415:14 444:24 454:11,11
milliliter 38:11 39:3 103:2,21 127:12,25 131:25 140:15 140:16 308:5,6 308:7 312:8,9 331:8,9,10 360:20
milliliters 100:25 101:1 132:4 137:14 137:15 139:7 294:23 429:25
millimeter 304:11
million 111:11 120:16 265:11 395:10
mind 185:13 266:1 355:23 416:11 443:3
mine 167:20 429:9
minimal 110:13
minimize 420:16 420:25 421:3
minimizing 261:14
minor 215:6
minus 219:16 224:16 303:20 305:24 306:2,2 330:15,25 336:1,1,15,16 337:20 338:10 338:15,23 339:1,2,3,22 339:23 343:4 345:8,9 346:24 346:25 349:15 349:16 350:10 350:20,21 351:15 353:3,4 354:1,1,8,9 355:9 357:15 361:11 362:13
minute 249:4 444:12
minutes 99:6 191:8 217:16 292:17,22 446:16
miraculous 144:23
mischaracteri... 28:20 36:9 51:24 55:11 56:15 60:1 84:15 101:10 110:10 120:3 132:22 136:13 142:4 143:4 147:19 201:3 205:14 256:21 258:7 259:13 285:21 302:2 303:12 304:6 323:22,24 324:19 329:14 333:8 335:20 344:10 367:7 368:25 375:5 376:4 386:6 389:24 400:12 431:11 441:18 445:13
misleading 112:2
missing 65:21
misspoke 48:6 277:25 392:24
misstatement 17:13
misstates 444:7
mistake 150:15 410:7
mistaken 249:2
mistakes 47:25
MIT 63:22
mitochondrial 94:24
mL 219:16 220:22 236:25 237:11 293:19 297:12,15 298:6,20 301:16,19 302:14 304:4 304:19 305:25 306:3 308:18 308:18,19 309:2,3,3,17 310:19,20,21 312:17 313:15 313:16,16,18 313:18,19 314:17,18,18 315:6,8,16,16 316:1,3,7,19 319:19,24 320:4,9,12,12 320:13,15,20 320:20,21

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 494 of 524

321:14,15,15 321:21,25 327:22 328:10 331:18,22 332:6 334:11 334:22 335:10 335:11 336:16 336:16 337:2,2 337:3,3,3,4,6,6 337:6,7,7,7,8,8 337:9 338:3,6 338:20,24 339:2,3,19,23 339:23 340:23 340:24 341:2 345:8,9 346:25 346:25 349:17 349:19 350:20 350:21,23 352:1,25 353:3 353:4 354:1,2 354:8,9,17 355:7,9,17,19 355:20 356:1 356:15,17 357:15 358:2 360:3,9 361:12 362:1 363:3,7 363:15,18 364:11,17 365:17 366:6 367:13 402:3
mm-hm 14:13 87:12 137:9 140:11 324:13 326:1 330:7 349:9
models 383:5,24 384:13,18 385:10,23 386:22
modification 459:7
modified 243:24
modify 458:16 458:20
moieties 244:15
mol 244:13
molecular 83:2,5 189:4 235:18 236:4 243:1,3 244:5 250:18 252:1
molecule 234:5,8 234:16 239:20 244:11,14 251:23
molecules 97:18 234:3,7,17 239:17,18,24 244:9 251:22
moment 90:15 125:5 133:9 196:13 256:20 266:2 270:6 276:16 305:1,5 306:13 310:4 449:9 450:2
monitor 152:20
monitored 408:15 410:19
monitoring 407:8,9 408:12
monkey 372:23
monkeys 417:6
monoclonal 243:18 250:17
month 134:5,7 145:20 161:21 162:6,10 168:11 261:9 261:11
monthly 145:19 162:22 273:1 274:5 399:20
months 18:24 19:3,13 25:3 56:20 62:4,11 134:6 145:21 392:5
moot 231:6
morning 9:18 11:6,7 43:18 46:17 115:7
motivate 248:1 249:19,20 400:7
motivated 218:23 219:5 220:10 224:5 248:11,13 249:8 265:17 265:19 297:8 311:2,20 370:25 373:16 399:13 431:8 432:1
motivation 171:4,12 220:18 258:12 260:24 261:2 286:2 369:2 451:11
mouthful 425:10
move 209:16 333:1 387:3
Mu 430:12,13
multi 200:14 205:24
multidisciplin... 20:9,18,23 21:9 54:21 55:1,6 57:6,9 57:23 197:15 198:12,15 200:15,19,24 201:16 203:9 203:12,15 205:1,12,20,24 206:6,15
multidisciplined 207:1
multilayered 88:18
multiple 91:5 107:11,25 117:19 141:8 149:9 156:12 157:6,7,9,17 157:18,21,25 169:5 270:19 271:6 303:6 363:10 377:15
multiplied 314:21
multiply 315:13 331:23
multiplying 315:15,16
mutual 287:1,5

N

N 226:10,10,10 412:5,5,5
name 9:7,19 11:8 16:1 18:12 23:12 228:23 435:11 435:11 462:2 463:8 464:2,4
named 434:12
narrow 32:11
natural 14:7 95:5
nature 156:25 408:14
near 98:17 199:23 355:13 355:18,19
nearly 43:18
nearsighted 103:15
necessarily 7:10 34:3 84:10 90:19 116:24 117:8,14 118:25 134:19 279:1 326:11 335:6 414:5,13 436:21 439:24
necessary 185:20 295:5
necrosis 188:16
need 19:4 31:10 34:3 47:5,12 47:13 52:23 53:4,7,11,16 70:3 73:18 77:17 90:21 94:19 95:16 108:14 121:24 136:1 137:22 139:1,1 145:22 146:4,5,21 147:1 161:14 182:20 195:13 198:13 213:15 213:15,19 232:13 236:19 240:4 242:18 245:16 263:22 290:6,7,11 293:8 302:3 303:1,4 306:12 315:1 316:24 354:11 361:21 362:3 364:15 368:10 370:2 388:2,19 396:2 421:11 431:16 436:17
needed 54:2 261:9 273:16 273:25 280:20
needing 147:4 365:24
needle 176:12 177:18,18 179:12,15 181:7 190:23 295:22 296:10 322:8 356:24 366:1 420:17 420:22,24 421:10,12,13 421:19,22 422:1,2,7,13 423:1,4,21 424:1 444:22
needs 151:19 388:18 414:10

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 495 of 524

negative 181:24 182:8 264:1
negatively 89:4 89:17,24 90:6
negatives 121:8
neighborhood 158:22
Neil 4:4 16:6,9
neither 58:2 389:16 461:14 461:17
neoplasia 149:9
neovascular 151:15,21 226:23 249:22
nerves 88:20
neural 232:1
neurochemistry 64:20
neurology 75:4 75:4,6
never 11:21 12:9 13:2,3 40:12 127:8 128:13 131:8 136:1 142:11 143:19 145:22 159:10 162:7 178:14 366:25 432:10 433:5,7
new 1:18,18 2:6 2:7 9:3,3,12,12 11:2 19:24 68:23 79:9 156:2 182:21 189:6 231:25 265:10 394:7 395:9 397:5 398:7 461:3
newer 126:8
Nguyen 272:9 272:15
night 44:18 46:17
nine 135:7
nitty-gritty 73:23
nod 14:12
Nodding 32:18
non-lawyer 223:11
non-operating 78:11
non-prefill 177:14
none- 8:5,10,15 8:20
Nope 246:12
normal 64:12 104:1,4 126:1 126:17,24 131:24 132:18 136:18 228:19 229:15 230:20 231:1,15 232:4 232:13,21,22 233:14,19 416:21
normally 115:4 366:15 411:10
normalness 178:20
Notary 2:10 11:1 461:3,24 463:25
NOTE 7:9
noted 407:7 442:10 463:17
notice 14:16
noticing 462:13
noting 353:24 462:13
notwithstandi... 396:17 398:9
Novartis 164:17
November 68:19
number 19:3 31:9,13 32:5 40:23,24 41:3 54:4 69:25 175:11 191:8 191:14 198:1 219:18,22 235:6 243:8 251:6 303:24 309:23 353:19 373:3 393:23 455:13,20
numbered 337:24
numbers 41:2,6 209:23 317:13 355:3 455:10 455:11,24
numeral 229:21 448:13
numerical 56:4
numerosity 55:15
numerous 20:8 20:10,17 54:13 338:22 440:22
nurse 138:15
NW 1:23 463:2

O

O 226:10,10,10 412:5
o'clock 225:24
oath 15:20 428:3 458:16 459:10 460:2
ob 212:24 450:13
object 14:15 168:4 256:18 342:25 343:1 343:12
objecting 28:23
objection 26:20 27:11 28:19 30:25 35:14 36:8 37:22 39:10 44:9 45:11 51:23 55:10 56:14 59:25 81:11 82:7 84:14 86:5,24 90:10 90:14,17 91:2 94:16 101:9 104:14 108:2 110:9 114:25 116:10 117:1,7 117:12,22 118:18 119:11 119:24 120:22 121:16 122:14 123:7 126:20 127:15 131:20 132:21 133:6 134:14 136:12 137:16 138:9 139:9 140:17 140:22 142:3 143:3 144:8 145:15 147:18 148:8 150:21 158:14 159:6 159:23 161:23 163:18 165:10 166:8 168:13 169:16 170:7 170:16 171:25 172:24 173:21 174:23 180:5 180:24 181:18 182:2,11,14 184:2 189:18 190:3 193:13 195:12 196:21 199:18 201:2 201:24 202:7 205:13 206:7 209:13 222:10 236:6 237:25 242:5 256:21 258:6,25 259:12 260:13 262:17 263:19 268:8 282:8,24 285:20 292:23 301:17 302:1 303:11 304:5 304:20 314:23 316:21 322:25 323:21 324:18 325:15 326:7 329:13 331:14 332:3 333:7 335:5,19 337:16 344:9 346:4 348:9 358:5 360:22 366:11 367:6 368:24 373:19 375:4 376:3 386:5 389:23 390:18 400:11 403:10,15 414:3 415:3,21 416:24 418:13 424:25 431:10 438:2 440:5 441:17 443:9 444:6 445:12 445:24 451:13 452:21 458:18
objections 14:17 45:23 90:16 117:10,12,23 444:16
objects 14:21
obligation 212:25 213:1,2 213:5
obliged 355:2
obliquely 185:12
observations 141:9
observed 179:6 281:19
obtain 29:17 155:10,13
obtained 29:13
obtains 66:22
obvious 20:21 35:3 210:12,24 211:5 214:15 214:22 215:1 215:10 220:4

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 496 of 524

222:22 223:4
223:10,16,19
237:23 302:25
303:9 331:19
361:20 369:5
377:6 448:12
448:19 450:13
451:25
obviously 96:20
137:24 158:17
196:11 205:21
206:16 217:15
obviousness
33:1,25 34:22
217:1,7 237:17
305:9 323:15
329:1 332:8
occasional
145:21
occasionally
73:11 191:16
occlusion 36:18
36:19 37:13
occupying 103:7
occur 70:7 89:7
115:14 157:25
264:12
occurred 401:4
occurring 98:6
occurs 191:16
October 68:19
ocular 134:8
393:24
odds 284:13
off-label 162:5
186:25 188:5
252:12,13
253:15 254:10
255:3 267:11
off-target
261:23
offer 151:25
194:22 195:4
204:7 425:19
426:5
offered 48:16
68:22 194:18
354:19 355:4
395:11 432:15
433:13 434:3
offering 214:10
offhand 250:23
office 1:1 169:5
433:1 462:8,16
official 75:2
326:24
oh 80:5 162:24
221:19 238:14
254:18 293:25
308:10 343:14
359:15 408:13
413:11 430:11
okay 12:11,15
12:20 13:10,22
13:25 14:24
15:8,15 16:5
16:19,25 17:25
18:4,14,15,21
19:11,16 20:3
20:16,22 22:14
23:4,15 24:1
24:11,15,23
25:19 27:6,16
28:4 29:15
30:5,11,18
31:4,8 32:1,8
32:15,21 33:2
33:12 34:15
35:9 37:4,15
37:25 38:6,13
38:19,25 39:6
39:14,15 40:10
40:14,19 41:10
41:14,18,22
42:3,7 43:4,13
43:21 44:12,23
45:8 46:14,23
47:7,18 48:2,5
48:11,19,23
49:14,18 50:9
50:20 51:2,8
51:13,17 52:1
52:6 53:1,10
53:20,25 54:8
54:12 55:5
57:21 58:10
60:3 61:13,23
62:10,19 63:1
63:10,14,23
64:2,11,15,24
65:4,17,24
66:5,17,23
67:5,18,25
68:6,17 69:1
69:12 70:9,14
70:18 71:1,5
71:20 72:15,19
74:9,20 76:3
78:13 79:5,21
80:1,15,23
81:2,6,23 82:4
82:24 83:23
84:7 85:10,11
85:18 86:2,19
87:6,21 89:14
90:24 91:15
92:23 94:6,8
94:22 95:1,12
95:18,19 96:3
96:7,15 97:7
101:13 102:14
103:4,8 104:10
104:23 106:14
106:15 107:8
107:22 108:19
109:1,5,13
110:16 111:16
114:13 116:3
116:21 117:17
118:6,13
119:14 120:18
122:3 123:3,20
123:21 124:1,5
125:18,23
126:6,12,16
127:10,20
128:6 129:7
131:15 132:6
132:11,15,24
133:23 137:4,8
140:5,10 141:1
142:24 144:1,2
145:3 146:17
149:19 150:7,9
150:12,15,17
150:18 151:9
151:10 153:16
153:21 154:19
155:9 156:6
157:8 158:10
159:2,16
160:13,14
161:19 162:12
164:23 165:7
166:2,22 167:4
167:9,17,23
168:7 169:12
170:3 171:18
172:18 173:12
174:12,25
175:20 176:3,8
177:3 178:7
179:3,9,20
181:11 183:1,5
183:11,22
185:3,14
186:10,16,17
187:22 189:9
189:14 190:14
191:21 192:1
192:13,18
193:5,9,16
194:2 195:7,18
196:10 198:18
198:24 199:4
199:13 200:5
200:20 201:18
202:15 203:10
203:16 204:3
204:14 205:6
205:18 206:2
206:11 207:5
207:21,23
208:2,6,17,24
209:8,18 210:1
210:6,15,20
211:11,16
212:2,6,12
213:23 214:5,8
214:12 215:16
215:23 216:2
216:11,23
217:3,11,17
218:15,16,20
218:25 220:6
221:14 222:13
222:18 223:1
224:1 225:17
225:23 226:4
226:15 227:7
227:12,22
228:1,5,18,24
229:7,12 230:6
230:8,10,16
232:5,7,11
233:2,16,23
234:25 235:12
235:17 236:10
236:21 237:1,7
237:12,19
238:2,8,17,21
239:2,6 240:1
240:7,11,18
241:2,24
242:16,25
243:5,11,12,25
244:4,16,21
245:6,17,20
246:5,13,20
247:1,12,18,24
248:21 249:10
249:12 250:6
250:13,24
251:7,20
252:14 253:17
254:19 256:13
257:17 258:16
259:24 260:7
262:5 263:11
264:5 265:15

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 497 of 524

268:1 269:1,7 269:11,21,24 270:5,8,9,25 271:4,8,25 272:6,10,19,23 273:4,11,19 274:4,10,19 275:22 276:5,8 276:13,15,25 277:3,4,9,18 278:6,12 280:8 280:15,23 281:23 282:2 282:19 283:22 284:10 285:11 286:11 287:7 287:12 288:6 288:15,21 290:2,4,17 291:2,7,18 292:6,16,20 293:5,10,21 295:25 296:20 297:6,21 299:2 300:3,10,15,22 301:11,22 302:5 303:3,25 304:14,22,25 305:3,4,4,8,13 305:15 306:4 306:23 307:6 307:12,13,24 308:11,16,25 309:8,16 310:13 311:10 311:14,22 312:2,15 313:3 314:7,15,25 315:5,10 316:10 317:3,8 317:21,24 318:7,11,15 319:12 320:7 320:16 321:2,9 322:11 323:3 323:16 324:6 324:12,24 325:9 326:2 327:4,6,12,18 327:24 329:3,9 330:8 331:5,16 331:20 332:21 333:4,19 334:1 334:5,13,16,24 336:3,7,20 337:1,13 338:1 338:18 339:7 339:18 340:11 340:21 341:5 342:11,20 343:10,15,23 344:4,24 345:4 345:18,25 346:21 347:17 349:1,4,10,23 350:16 351:2,8 351:17 352:4,8 352:22 353:2,7 353:18,23 354:5,12 355:5 355:16 356:4 356:12 357:5 357:13 358:9 358:23 359:12 359:17,23 360:17 361:6 362:2 363:12 364:9,16,22 365:7,11,16 366:4,24 367:3 368:13,20 369:8,14 370:8 370:12,22 371:5,9,16,19 371:24 372:6 373:13,25 374:21 375:8 375:14,23 376:7,18 377:14,18,22 378:2,3,7,17 378:25 379:14 379:16 380:4 380:10,14,21 380:24 381:14 382:2,18 383:1 383:14,18,23 384:23 385:7 385:13 386:19 387:6 388:22 389:4,14,19 390:2,14,21 391:8,9,12,16 392:8,11,20,23 393:7,10 394:11 395:4 395:23 396:8 396:15 397:6 398:3,15,21 399:2,9,17 400:21 401:1,9 401:19 402:12 402:23 403:2 403:21 404:14 404:20 406:8 406:17,22 407:16,22 408:5,10,17 409:3,9 410:2 410:14 411:9 411:13,17,23 412:12,17 413:11,12,16 414:15,19 415:10 416:12 418:4 419:6,9 419:15,20 420:2,5,12 421:17 422:9 422:15 423:12 423:17,24 424:8,9,20 425:5,18 426:8 426:19 427:15 427:25 428:15 429:10,16,20 430:4,13,15,22 431:6,14,22 432:4,9,14 433:11,17,23 434:7,11,25 435:8,17 436:13,23 437:3,8,19 438:24 439:3 439:15,21,25 440:19 441:2 441:12 442:11 443:6,17 444:1 445:8 446:8 447:7,14 448:22 449:1 449:16,25 450:7,14 451:7 451:23 452:10 453:3,15 454:2 455:15 456:2 456:12,17 457:2 458:7,12 459:8,13,20,25 460:4

old 153:19
oldest 75:8
once 34:16,19 51:10,11 53:1 146:19 161:21 162:6 177:4 248:14 277:23 326:22
One-six-nine 412:15
one-tenth 298:20
one-to-one 239:25
one-twentieth 312:13
one-week 133:15 134:4
one-year 156:19 246:18
ones 50:22 164:9 227:15 232:3 337:1
oneself 206:25 207:1
open 154:17 267:1
operating 138:14 142:18
operation 73:16
operations 315:23
ophthalmologic 130:25
ophthalmologi... 75:15
ophthalmology 6:6,10,15,19 16:10 66:16,19 66:25 67:16 68:24 75:1,7 79:13 95:24 106:20 124:24 197:16
opine 376:10 387:9 450:18
opined 254:15
opinion 29:11 48:12,24 49:2 49:6,10,15 50:5 57:17 116:13 135:13 142:1 144:3 193:17 194:23 195:4 198:20 198:25 200:4 203:20 204:7,8 209:11 214:10 215:24 218:22 219:4 220:13 222:20 224:3 225:20,21 257:18,21,25 259:9 260:7 263:2,9 265:16 283:23 284:1 286:22 287:20 294:17,21 296:21 297:7

301:13 304:2,9 304:17 305:9 305:16,17,21 313:14 324:14 327:7,7 334:20 338:2 344:8,14 347:18,25 348:5,20 359:7 360:12 364:23 366:21 373:14 376:1,20 377:4 377:6 381:9 399:12 407:14 413:20,23 422:2 425:19 431:7 432:15 433:13 442:15
opinions 27:9 29:3,4,7,8,9 30:9,20,21,21 30:22 48:9,15 48:18 50:15,24 56:10 57:1 58:12 59:10 162:13 185:21 186:13 194:5 194:19 201:11 208:8,12 209:10 211:9 213:13 218:11 218:17 237:2 237:16 240:21 241:17 244:2,7 254:14 256:11 256:17 258:8 258:19 264:11 286:20 288:11 290:7,9,21 291:4,24 297:23 318:9 322:13 382:13 417:20 434:3 442:17 447:11 452:2 454:4,15 457:19
opposed 189:8
opposite 246:12 429:1
optimal 113:19 114:15 296:16
optimization 445:9
optimum 366:20
option 77:19 462:10,11
optional 139:21
orally 407:3
order 47:14 50:23 87:1 88:11,16 146:22 159:11 191:12 224:6 235:22 320:16 366:9 377:9 395:9 425:13 427:13 445:6 451:25
ordinarily 116:4
ordinary 19:21 34:5 35:3 57:12,18,24 58:4 67:22 68:2 143:15 197:13 198:10 198:14 199:9 199:15,21 200:8,13,17,22 201:7,23 202:5 202:13,18 203:8,13 204:6 204:9,19 205:8 205:23 211:1 212:8 285:6 288:4 299:18 303:23 331:4 337:21 339:16 340:6 343:6 344:23 345:1 345:16 346:18 347:14 348:4 348:18 358:24 359:4 364:4 366:21 381:5 383:12 395:12 395:13 404:10 405:11 440:13 446:3 448:15 454:8
organ 86:12
organic 420:1 425:8,15,23 426:12 427:8 427:21,22
organisms 80:20
orient 455:6
orientation 211:17
original 5:16 150:4 167:19 171:11 281:3,7 281:24 462:12
originally 162:11
Oum 6:13 106:18 107:2
outer 87:15 88:22
outlined 174:11 267:25 329:2 359:2 404:3 432:2
outs 386:21
outside 46:25 47:3 50:22 173:22 181:16 181:17,19 222:11 293:7
overabundance 232:23
overall 112:2 275:1
overdosage 135:13 399:7 399:11 400:16 400:18 408:13
overdosages 137:2
overdose 132:8 132:17 135:3 141:18,23 326:9 401:3 407:2 410:7
overdoses 176:22 325:2 399:23,25 400:5 402:10 402:20 403:9 405:2 410:17
oversimplifying 76:23
owe 178:25
owner 1:8 9:20

P

P.C 3:4
p.m 226:6,13 306:16,20 411:25 412:9 446:23 447:2 460:11,14
P1GF 227:24 229:1,9,10,13 229:14,25
P1GT 228:2
packaging 177:17 189:24 257:13
page 5:3 6:4 7:4 8:4,9,14,19 32:4 40:15,23 41:3,6,11 42:9 82:11 109:4 113:7 158:3 209:18,21,23 250:10 273:13 276:17 277:6 370:14,18 371:7 389:12 391:10 399:2,4 402:15 413:10 447:24,24 448:5 449:10 455:5,9,13,17 455:19,22,23 455:23,25 456:1,18 462:13 463:6 464:8,10,12,14 464:16,18,20 464:22
pages 32:4 231:14 372:17 375:10 463:11
painful 421:14
Palmer 67:3 252:21
panel 241:9
paper 12:13 26:18 27:2,7 28:15 126:22 131:16,23 132:16 133:21 156:4,7,10,24 157:20 158:6 246:14,19,21 275:24 277:7 315:2 316:25 378:1 385:2 386:3 391:2 416:9 438:16
papers 154:24 156:12 157:10 157:14 158:7
paperwork 12:24
par 359:6
paragraph 42:9 48:3,5,6,7,8,25 49:3,7,11,19 84:9 87:11 106:8 113:8 133:24 197:2 197:10,12 198:22 199:1,2 199:5,24 200:7 200:12,25 201:8 202:13 203:19 204:8 204:11,18 205:11 209:23 210:2,7,22

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 499 of 524

211:21 212:19
216:10 218:18
219:2,3 228:13
231:11,13
233:5 234:1
238:8 240:8
242:22 243:12
244:18,22
245:21,22
250:11 269:25
270:6 271:10
271:15 272:4
272:11,21,24
278:11 281:14
303:17,22
305:11 307:8
308:1,2,12,23
311:24 315:4
319:4 320:13
320:18,23
321:3 323:9
329:12,24
331:11,11,23
333:23 334:15
336:9 339:13
339:14,17,19
339:21 340:12
341:8,12 343:8
345:14,14,22
346:3,8,9,14
346:15,19,24
347:16,19
348:5,23,25,25
349:5,5,11
352:6,9,11,12
352:13,14,18
352:20,20
353:2,9,21
357:24 358:11
358:16,17,19
358:21 359:14
361:7 371:7
373:4 374:22
379:1,18,24
380:22 382:24
383:3 385:8
387:7,22 389:6
389:16 390:3
390:10 391:13
393:11 410:1
412:12,19
413:3,9 429:18
429:21 430:10
431:19 448:6
448:10 452:11
453:24 454:3
454:14 456:15
456:18,22
paragraphs 41:5
235:15 274:17
342:13,16
359:1 455:3
457:1,3
parameters
283:10 433:25
445:10,15
Pardon 28:22
404:24
parse 205:17
part 50:4 54:20
56:24 57:18
59:18 73:11
135:4 177:1
178:5 180:8
181:25 198:21
199:2,14,16,17
200:1,14
201:15 203:25
280:24 281:16
281:17 341:24
354:23 368:18
368:21 369:6
374:20 400:4
426:1,1
partially 234:14
327:14
participant
128:2
participate
155:20 205:11
participated
20:7 154:20
200:16,23
particle 184:12
particles 179:6
particular 64:9
78:23 90:11
99:11,12,14,15
105:4 107:12
126:25 138:24
159:18 176:1
262:6 346:7
406:6 422:2
particularly
457:14
particulate
185:1
particulates
181:6 182:1,10
182:16,20,23
183:3,8,17,19
parties 461:16
parts 211:13,17
party 18:8
pass 159:11
patent 1:1,2,8
1:11 9:20
11:19,20 12:6
12:8 31:6,9,18
31:19 32:3,10
32:24,25 33:5
33:10,14,24
34:2,7,21,23
37:1,19,24
38:2 39:9
199:7 210:11
210:18 212:1
219:14 220:4
222:23 237:9
237:14 294:12
297:2 302:3
303:16 306:8
311:9 320:25
323:12 324:1
324:22 328:6
329:8 335:7
337:15 341:17
342:4,10
343:21,25
344:2 347:9
348:14 351:6
351:12 352:12
355:4 360:15
360:21 367:10
367:12 428:25
432:21,22
433:1,3 450:12
patent's 346:1
patentholder
362:8
patents 32:6
35:25 237:21
294:13 362:6
377:5
pathway 122:24
328:25
patient 72:8
77:7,10 78:1
103:18 108:16
130:23 134:25
137:6 140:8
145:1,12,13
146:1,8,11,20
147:16 148:2,5
148:10 149:1,4
150:25 151:11
151:14,19,21
152:2,20 153:1
153:5 160:16
160:18,22
161:4,16
163:13 169:1
169:23 186:5
186:18 187:18
191:8,12
232:17 253:8
262:2 281:12
325:5 366:3
374:18 407:3
407:18,19,24
408:2,14
420:19 421:1
429:25
patient's 149:5
154:2 184:15
187:10 233:20
258:14
patients 20:1
49:23 69:4,11
69:14 71:7
87:5 98:5
100:7 103:20
108:12 133:16
133:25 134:4,5
135:8,25
136:21,21,23
139:8 140:2
143:22 145:18
145:19,21
146:4,5,8,12
146:13,24
147:2 148:11
149:21 151:3
153:14 155:6
161:12,13
163:3,23 166:5
168:8 186:22
191:17 215:4
219:20 221:1
221:13 225:9
238:16 252:22
253:13 263:8
266:23 269:20
270:22,24
271:1,5 273:5
273:13,24
274:4 277:11
277:21,22
278:2 279:13
280:18 282:16
284:19,20,21
284:22,23
285:25 367:18
367:21 376:15
378:14 387:14
388:3,19
401:11,16
407:19 410:18
patients' 70:21
426:10

pattern 138:23
patterns 138:6
Pause 305:7 310:11 372:12 390:23
pay 155:21
peak 99:17 100:12,14,20 101:3,7,25 102:4,10 104:12,19,25 105:15,20 106:3,10 384:8 384:9
pediatric 75:4
peer-reviewed 386:10,18
pegapt 239:17
pegapta 239:18
pegaptanib 238:5 432:9
PEGylated 166:12,13 238:24
pen 26:18 27:2,7 28:15
penalties 43:11
penalty 15:22 42:12
people 21:3 23:13 58:1 85:22,23,24 103:11,12,15 103:25 135:5 135:22 143:9 162:8,19 299:23 325:6
people's 103:11 159:21
per-hour 21:24
percent 140:2
perfectly 136:4 389:17
perform 73:10 74:1 76:9,14 123:19 127:3 128:12,19 129:5 130:11 131:7 152:17 240:24 280:2 310:16 317:22 440:16
performance 171:14 325:8
performed 72:16 73:7 80:8 85:13 96:13 128:16 129:1 129:16 130:8 170:25 369:7 381:25
performing 230:20,22
period 65:14 131:6 134:8 381:22 433:4 462:14
periods 161:14
peripherally 457:14
perjury 15:23 42:12
permissible 183:9 330:20
permissive 388:16
permit 319:22 423:2
permitted 91:25 261:8 290:22
person 19:21 23:16 34:4 35:3 36:21 57:12,18,24 58:4 67:22 68:1 75:10 116:4 119:8 133:1 134:10 143:15 144:4 148:18 152:15 153:24 157:12 159:20 162:15 191:23 193:18 195:10 196:17 196:24 197:7 197:13 198:10 198:14 199:8 199:15,21 200:7,13,17,22 201:6,23 202:5 202:12,18 203:7,13 204:5 204:9,19 205:8 205:10,23 208:1 219:10 221:3 222:3 223:20 237:3 247:25 248:13 249:16 259:9 263:4 285:6 288:4 294:5 296:3 299:17 303:23 304:18 311:1 316:12 316:12,15 317:20 331:3 337:21 339:16 340:6 342:3 343:6 344:22 344:25 345:16 346:18 347:13 348:4,18 352:24 358:24 359:4 364:4 366:21 369:17 369:25 370:23 373:15,17,22 377:7 381:5 383:12 386:13 395:12,13 399:13 400:8 404:10 405:11 425:13,20 431:8 432:1 438:21 440:13 446:3 454:8 456:8
person-by-per... 105:9
personal 69:22 154:13 435:13
personally 62:22 128:4 162:7 176:19 177:1 201:5 440:1 442:22
perspective 96:21 383:20 421:21
pertaining 185:8
pertains 58:5
pertinent 254:24 256:16
petitioner 3:3 10:9
Petitioners 1:5
Petra 4:2 10:1
PGR2025-00085 1:10
Ph.D 198:1 202:24
phakic 113:22 114:18
pharmaceutical 38:9 198:2 202:24 239:11 336:13 345:6 349:14 350:19 424:12
PHARMACE... 1:7
pharmacies 267:12
pharmacist 138:16 253:11
pharmacokine... 384:21
pharmacokine... 113:4 385:4
pharmacologic 142:23
pharmacologi... 197:24
pharmacology 112:13 114:2
pharmacother... 86:10
pharmacy 253:9 255:5 256:1 257:2,4,5,15
phase 273:13 276:19 277:6 277:10 280:17
Phil 252:21
phone 3:9,21 309:25
photography 110:14
photoreceptor 88:4
photoreceptors 88:3,22
phrase 122:11 217:15 264:13 266:17 299:11 347:12 396:21 396:23 459:4
phrased 162:11
phrases 451:22
physical 422:22
physically 155:15
physician 10:6 49:23 58:6,6 71:19 157:11 178:4 364:4 406:4,7,9
physician's 169:4
physicians 69:25 142:20 188:19
physiologic 230:23
physiological 228:20 230:20 231:1
pick 175:17 252:16 272:14
picked 367:4 403:24

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 501 of 524

piece 218:7 321:22 362:14 379:17 418:22
piecemeal 65:25
pieces 35:12 377:15 383:21
pigment 87:17 87:22 88:1,9 88:14,15,22 89:4,18,25 90:7 91:19 93:6 94:12 112:23 115:23
pigments 88:4
pill 115:7
pilot 175:14
place 9:11 50:2 51:6 52:20 53:9 60:7,16 60:18 61:1,3 61:19 87:9,10 153:22 154:3,5 154:6 196:8 208:15 366:20 397:14 433:3 461:12
placed 39:16
placement 346:14
placental 228:23 230:7,9,13 231:7 232:15 232:18 233:7 233:20
places 449:17
planning 95:4
plateau 146:24
platelet 227:18 227:23 230:3 230:18,19 232:15
play 206:24
please 9:16 10:16 14:2 15:6 20:20 22:7 30:24 31:1 48:4 49:19 55:22 58:21 84:23 85:2 89:20 91:24 92:1 105:23 145:7 182:4 216:20 227:9 275:10 307:7 348:1 350:11 386:25 391:10 412:15 419:7,24 429:17 431:20 436:4 446:6 455:2 456:22 462:6,11,12,15
PlGF 229:6,16
plucked 252:25 331:6
plugged 441:14
plural 156:25
plus 219:16 224:16 303:20 305:24 306:1,2 321:20 330:14 330:15,24 336:1,1,15,16 337:20 338:10 338:15,23 339:1,2,3,22 339:23 343:3 345:8,9 346:24 346:25 349:15 349:16 350:9 350:20,21 351:15 353:3,4 353:25 354:1,8 354:9 355:9 357:15 361:11 362:13
point 12:9 18:25 30:10 33:11 44:25 45:17 83:15 84:8 85:18 86:6,8 89:11 92:7 95:5,6 98:4 108:20 114:7 115:3 145:10 169:19 185:15 189:5 216:6 225:19,25 231:5 251:12 261:1 279:5,21 282:11 283:21 286:12 295:11 299:5 329:17 341:14 350:11 351:25 352:9 352:14 353:8 353:10,15 365:23 366:18 368:2 369:18 369:19 373:2 378:19 417:8 428:22 440:12 444:17,19 459:2
pointed 416:9 417:13 426:6 449:8,12 453:8 453:12
pointing 397:19
points 69:11 114:12 123:13 225:18
poor 267:13
population 134:25 136:18 139:24
portion 199:23 226:21 303:22 324:12 342:6,7
portions 55:3,8 96:18 453:9,13
POSA 67:21 163:16 197:14 198:22 200:1 203:18,20 205:3 212:9 218:22 219:4 220:9 224:2,4 224:8,14,18 225:4 239:7 249:7 262:8,11 263:2 265:16 265:19,21 266:20 267:2 296:24 297:8 299:4 307:14 308:20 309:10 310:21 311:19 312:10 314:9 314:11 315:12 318:12,19,24 321:4,11 322:15,22 323:5 324:14 327:8,20 329:25 334:16 349:12 393:16 403:7 412:19 413:5,19 426:1 429:22 430:16 430:24 443:19 444:4 457:5
POSA's 307:18
position 68:24 69:3 204:23 311:1 389:22
positive 175:18 264:3
possess 200:11 201:9
possibilities 205:25 206:3
possibility 187:1 293:17 435:23 435:25
possible 44:17 44:20 56:5 154:18 260:25 286:4 293:23 299:24 301:10 319:22 322:6 328:11 329:20 362:8 364:20 364:24 444:20 445:4,5
possibly 172:16 254:25
post 97:8
post-document 21:24
postoperative 152:24
potency 80:19
potential 77:18 86:17 91:20 94:24 135:14
potentially 34:13 99:7 180:23 354:23 421:15
pound 278:20 278:21
practical 65:14 75:12 76:11 298:25
practice 11:22 45:22 70:2 74:22 138:6,23 142:10 143:17
practicing 10:5 22:23
practitioner 20:15 35:23
practitioners 161:25 162:1
pre 386:23
pre-existing 34:25
pre-presentati... 156:20
pre-specify 317:16
preceding 42:8
precipitants 179:6
precipitated 297:4
precise 19:5 93:23 121:25 251:5 427:9

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 502 of 524

precisely 104:21 106:13 135:11 297:9 303:2 429:1
precision 62:9 236:2
preclinical 385:3 386:24
preclude 302:23
predicated 83:5 83:6 304:2,8,9 304:17
predict 146:15 146:18,20,23 149:24 161:16 174:8 383:6 384:13 385:23
predicting 174:5
prediction 384:5
prefer 145:1 158:11,21 300:7
preferable 429:23
preferably 222:5
preference 136:15 160:4 160:10 190:1 254:9
preferences 445:15
preferential 158:25
preferred 189:16,19,25 430:17
prefill 177:12 189:21
prefilled 176:17 177:12 181:5
prejudged 30:22
preliminary 156:18 174:2
prematurely 93:21
premise 162:15 263:9 285:13
preoperative 136:20
prep 23:1
preparation 21:23 22:1,3 47:20 59:19 176:20 181:4 203:24 204:1 208:16,18 256:2 381:22 409:17
preparatory 20:8,17 54:21
prepare 20:4 316:25
prepared 21:13 141:13 176:14 267:11
preparing 21:17 71:15 447:10
prescribed 189:20
Prescribing 7:6 247:8,21
present 4:1 97:18 109:5 119:17 139:21 173:4 176:18 241:1 405:16 409:1,7
presentation 156:17,19 381:12
presentations 143:12 154:8 155:21 156:13 160:7 162:1 239:14 405:20
presented 157:6 157:20 241:7 396:5 406:19
presenting 77:8 77:10 157:10
presents 78:1
preserved 106:1
pressure 191:5,9 191:13 295:24 299:24 312:24 366:2 367:20 374:17 401:15 409:21 421:4
presumably 232:19 274:20 282:1 283:8
presume 147:10 208:9,10 228:17,22 230:25 239:22 239:22,24 244:14 248:25 283:2 417:7 442:18,21 455:10
presumptive 139:1
pretty 15:2 150:13 433:7
prevailing 387:23 388:5
prevent 135:15 136:4 140:3 176:22
prevention 73:5 74:2 130:7 137:3
prevents 229:14
previous 112:10 116:15
previously 60:22 60:23 383:5 384:11,12,18 404:3
primacy 218:13
primarily 88:23 112:24 231:23 250:15
primary 158:11 319:19 323:25 324:22
principals 18:12
principle 408:1
principles 172:8 172:9
prior 17:16 19:6 19:7 29:10 35:7,12,24 56:8 58:23,24 105:25 148:14 156:13 169:5 171:8 174:4 210:3,9,9,17 211:1,2,23,25 212:14,17,20 213:11 214:1 214:25 215:8 216:19 217:23 222:6 224:9 243:21 246:19 262:8,9 263:12 324:11 328:8 368:23 385:4 404:7 439:12 439:13 440:17 448:14,16 449:3,19 452:7 452:14 453:1 461:4
priori 180:19
privacy 169:2
privilege 29:22 58:19
privileged 287:17,22
privy 361:3
PRN 264:16 266:19 395:1
pro 358:17
probable 381:23
probably 33:7 37:10 76:23 92:25 136:1 152:11 155:17 160:17 161:2,7 171:20 173:2,3 173:5 251:2 272:13 276:11 292:15 322:6 356:25 369:12 369:13 384:7 386:14 451:4 459:3
problem 16:22 135:12 214:21
problems 86:11 161:5 185:1 283:16 367:25
procedure 72:14 131:4 143:20 163:9 169:6,24 171:1 462:15
procedures 77:6 152:18 406:5
proceed 46:6 58:21 66:6 432:2
proceeding 31:11 318:6 433:14
proceedings 45:24
process 21:6 25:8 57:6 97:22 186:20 208:15 287:5 288:3 328:20 358:17 439:13 442:19 443:16 445:19 446:2
processes 203:23 232:8,21 257:8
produce 91:12
produced 379:20
product 189:7,8 216:4 264:22
PRODUCTION 8:8
products 188:1 363:21,24 365:22
professional 58:8 71:18 194:24

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 503 of 524

professor 16:9
profile 98:9 99:8 122:25 148:13 148:17 418:6
profiles 148:21
profound 191:13
project 419:14
proliferative 36:17
prolong 261:12 376:13 378:11 387:11,25 388:9,25
prolonged 180:17
prolonging 384:4
prolongs 380:2 388:13
promising 386:16
prone 136:25 148:12
pronunciation 125:22
proof 87:3
proper 177:16 177:19
properly 176:24
properties 170:13,20,21 172:12 197:25 219:23 346:11
property 423:9
prophylactic 73:3 74:2 128:13 130:5 130:16,23,24 131:13 134:20 134:21 135:11 135:19,20 139:2,15,22
prophylactically 72:21 129:21
prophylaxis 126:18 127:6 128:10 133:4 136:9,17,24,25 137:7 139:20 140:9
proposition 377:19
proprietary 21:6
prot 425:3
protein 19:25 38:15 179:21 179:25 180:4 180:11 181:9 181:16 182:19 182:22 184:12 185:4 193:10 193:19,20,24 194:7,15 195:9 195:16 196:19 221:22,25 226:21 266:6,9 267:15 301:14 303:7 304:12 304:16 356:22 419:25 425:4 427:24
protein-related 267:20
proteins 36:7 38:11 180:1 193:23 198:5,6 203:3,4 393:15 424:13
prove 380:1 388:12,17 427:14
provide 17:5 48:11,15 93:11 94:1,4,20 121:14,24 122:12 123:4 138:11 172:7 173:9 203:20 204:13 213:16 268:22 319:9 340:14 360:7 362:7 411:15 423:7 459:23
provided 41:24 179:13 200:2 203:19 212:10 323:13 329:11 359:25 404:15 409:25 411:16 419:17,18 436:6 437:5,9 438:15 456:8 458:22 459:10
provides 137:10 258:3 262:12 336:21 337:1
providing 61:11 172:15 338:13
proximate 444:24
proximity 51:21 62:7,12
proxy 101:17
psoriasis 148:4
pub 158:11
public 2:11 11:1 403:7 461:3,24
publically 16:2
publication 133:1 137:10 138:4 158:12 245:1,3,13 281:24 382:15 390:16 405:22
publications 143:8 255:25 402:13,16,19
published 35:24 127:5,21 156:3 158:5,7 246:16 246:17 265:3 328:6 383:5 384:12,18 385:23 391:17 391:25
pudding 87:3
pull 305:6
pulled 330:17
pulling 329:17
punishable 42:21
purchased 462:9
purpose 89:8 115:18 379:5
purposes 40:1 86:21 204:6 207:10 241:16 254:14 258:18 403:23
pursue 397:5
pursued 366:8
push 421:19 422:12 423:21
put 26:18 27:2,7 28:15 56:10 76:24 92:5 101:24 102:2 118:2 144:2 172:21 176:12 196:15 278:20 369:9 411:18
putting 105:11 105:14,17,19 337:20
pygmies 104:3,5 104:8

Q

Qu 4:5 9:24
quadruple 401:6
qualifications 198:21 199:1 200:12 217:9
qualified 202:11 205:11
qualify 187:11 210:9
qualities 327:3
quality 141:4 143:6,9
Quan 272:9,15
quarter 207:18
question 14:15 14:20 15:1,6 15:11 19:9,10 20:20 21:12,22 21:24 22:7 25:23 26:23 30:6 31:1 32:12,14 35:17 37:3 40:20 44:11,24 45:20 46:7 47:14 48:13 55:21 58:20 60:9 68:8 73:18 83:25 84:24 89:16,20 90:21 90:21 92:12,20 93:1 101:3,22 101:24 102:7 112:10 122:1 125:12,14 141:3,20 143:21 144:16 145:6 147:22 148:20 149:18 150:4,8,10,14 154:4 156:1 158:16,25 160:1 166:23 168:17 169:11 169:19 170:10 173:7 182:4 183:14 185:17 196:22 198:9 198:17 199:25 200:6 202:14 203:6 204:3 206:10,16 216:21 220:8 248:7,8,9 249:13,15 256:9 258:17 259:3,16,19 260:15 262:23 263:12 266:1 268:10,13 276:16,23 289:20 290:3 303:2 312:3,4

316:11 323:2 329:12 332:24 343:16,19 348:1 350:14 350:17 354:5 360:8,10 364:16 374:21 377:3 382:10 382:12 395:25 396:3 397:16 398:1 408:22 417:17 423:17 427:9 428:20 433:25 435:17 435:19 438:5,7 444:17
question's 329:3
questioning 446:12
questions 8:18 14:12 21:18 150:5 152:16 317:12 343:13 446:11 447:7 447:16 453:20 454:20 457:24 458:4,9,14,17 459:15,22 462:15 463:16 463:20
quick 146:12 390:21 411:19
quickly 15:2 99:1
quite 11:11 86:16 139:2 253:14 345:14 356:19 381:11 381:11
quotations 7:9
quote 7:11 88:20 353:24 354:7 448:17
quoting 351:17 354:14

R

R 226:10
rabbit 100:24 109:9 110:8,21 119:20 129:9
rabbits 74:14 101:18 102:16 102:17,18,25
race 104:6
radiation 114:4
raise 10:15 409:23
random 267:11
randomized 273:5 284:17
randomizing 277:11
range 103:12 180:6,8 222:1 251:3 296:16 299:13,14 306:1,1 309:14 312:5 328:16 329:18 330:13 330:16,18,20 330:24 331:2,7 332:11,12 333:15,21 334:6,7,9 336:22,25 337:23 340:14 340:15,19 351:12,13 353:3 354:18 355:3 361:18 362:8 363:24 367:17 426:3 445:2
ranges 302:17 302:18,22 303:6,8 304:15 319:22 362:15 367:5
ranibizumab 162:4,4 187:3 187:4,19 188:4 188:4 243:13 243:15,16 244:2,6,10 250:9 256:6 261:16,17 263:16 264:7 264:15,18 268:18 282:22 283:1,2 284:6 380:19 384:3 385:5 391:19 392:3,17 393:4 394:4 396:11 412:25 413:19 414:1,4,8,9,21 415:2,5,7,14 415:20 416:3,7 416:19 417:9 418:7,10 427:5 432:10 457:9
rapidly 424:14
rare 161:7
rarely 186:25
rarity 78:9
rash 92:4,11
rate 98:2
rationale 156:14
rats 417:6
re-read 348:1 351:11
re-review 240:25 241:12
reach 321:10
reached 12:9 17:9,10,19 18:16 34:19 99:17 384:8
read 7:10 26:17 27:3 28:16 33:14,16 34:22 34:24 35:10,19 37:18 43:2 50:7 54:10,16 54:20 55:25 58:14 84:25 109:11 128:22 130:21 156:4 159:8,21 160:4 160:5 195:22 196:7 199:22 213:9,20 248:3 248:6 270:6 272:1 291:20 305:19 339:17 343:8 344:1 346:23 347:15 348:5 350:12 370:1 413:14 419:23 426:25 428:8,11,13 440:7,9,11 451:9 456:17 458:23 463:10
reading 27:20 30:13 34:1 36:22 56:25 57:2 113:17 306:7 331:3 336:12 345:16 347:5,6,7 359:1 370:24 375:6 442:6 456:25 457:17
reads 82:15 125:8,15 249:9 270:7 276:20 277:2 392:12 392:25 456:20 456:24
ready 125:6 277:3 456:23 462:7
real 3:6 139:1
realize 195:21
realized 261:6
really 95:14 138:1,2 143:1 147:21 157:20 158:25 161:7 161:12 203:6 249:13 290:5 294:17
Realtime 2:10 461:2,23
reason 16:15 33:1,25 82:2 108:10 112:6 112:15 120:8 127:11 133:2 134:11 135:23 137:13 232:7 314:16 325:21 352:23 428:21 429:13 464:5,8 464:10,12,14 464:16,18,20 464:22
reasonable 19:23 120:20 121:14 122:12 136:6 152:4 219:6 221:6,8 221:16 262:13 285:7 317:1 354:20 356:20 357:4 364:5 366:22 412:21 413:6 451:1,11 456:8,9
reasons 151:3 257:1 267:24 311:16 404:2
recall 12:16,24 13:16 17:3,18 18:5,12,17 19:1 23:12 25:2,15,16,18 25:20,22 26:6 26:7,8,11,12 26:15,16 28:13 41:21 43:14,17 43:20 44:4,5 44:13,21 45:2 45:3,6,9 46:11 46:13,15,19,22 47:5,8,11 52:10 54:24 55:17 62:7 63:3,6 129:5

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 505 of 524

164:20 167:8 194:21 195:15 196:14 234:9 240:12 242:23 243:1,3 284:21 288:18,20,24 289:4,8 290:15 291:22,24 292:3,7,18,19 293:4 294:7 319:11 369:9 369:11 381:24 397:18 415:15 428:7,8 433:10 433:12,16,18 433:21 434:21 436:9,24 437:2 439:5,6,16,20 447:12 448:2 448:23 449:5 449:14 452:15 452:24 453:10 453:12,18 458:23
recant 458:15
receive 25:14 26:2,3 145:13 145:18,19,21 149:22 273:6 277:12
received 25:17 25:21 52:7 53:14,18 59:12 62:20 215:4 271:2,6 321:21 407:19 408:12 441:13
receiving 58:25 152:8 169:6 274:5 277:21 278:3 407:25
receptor 226:22 227:1,4,6 228:14
receptors 228:10
recess 124:9
226:8 306:18 412:2 446:25
recharacterize 167:18
recited 222:22
recognition 261:24
recognize 31:15 79:22 96:4 125:3 368:6,8 368:9 419:9
recognizing 160:22
recollection 18:19 27:17 51:15 62:1,6,9 235:22
recollections 20:13
recombinant 126:8,10
recommend 160:17 369:16
recommendati... 100:6
recommended 370:15,20 409:18
record 7:10 9:6 9:17 90:16 117:11 124:8 124:12 194:4 226:7,14 229:25 306:11 306:17,21 310:5,8 412:1 412:10 446:19 446:24 447:3 460:12 464:5
recorded 463:16 463:21
records 31:24
recount 382:8
recover 93:20
recumbent 243:17
recycling 88:3
red 92:8,8
redirect 446:13 446:15 457:25 459:3
redo 298:24
reduce 165:15 171:4 393:18 425:14
reduced 94:13 165:5
reduces 229:9
reducing 384:6 420:6,10
reduction 163:15 277:20 376:14 378:13 387:13 388:2
Reese 65:7
refer 67:21 77:13 196:23 216:6 244:18
reference 39:2 57:13 60:21 109:20 132:22 213:18 250:20 269:15 270:1 384:17,24 385:16 397:24 424:21 426:7 453:1 454:21
referenced 112:11 222:6 385:17,19 398:8 416:8 462:7
references 35:24 38:15,22 220:11 222:21 245:15 332:23 379:11 440:10 442:7
referencing 56:5 56:23
referring 12:19 20:24 21:10
33:20 39:21 153:7 216:7,9 245:8 283:3 308:2,4 339:15 340:4 343:4 345:10 353:16 369:20 370:6 371:17 431:15 431:19
refers 357:14 371:25
reflect 204:8 319:14 384:18 416:4
reflected 7:9 211:18
reflects 407:12
refresh 24:19 194:9 195:14 240:4 269:22 270:15
refreshed 368:11 370:3
refrigerator 101:25 102:1,3 188:2
refrigerators 295:5
regard 33:9
regarding 21:6 36:25 45:23 142:9 143:12 145:6 157:1 159:13 181:3 185:8 194:1 216:21 241:23 256:11 259:10 305:16,18 394:13 406:19 450:17 454:4 454:20 457:7 457:20
regardless 99:17
Regeneron 1:7 4:3 9:14,20 10:2 11:10
164:10 171:15 223:13 405:15 406:14 410:15 462:1 463:7 464:2
Regeneron's 31:6,18 377:5 405:20
regimens 197:19
region 243:21
Registered 2:9 461:1,23
registration 283:4,15,19 382:7 408:2
regulatory 75:20
reinject 114:24
reinjecting 108:15
reinjection 113:20 274:25
rejection 114:15
relate 83:17 232:3 266:1 342:13,17
related 35:25 37:23 38:1 58:6 77:5,6 100:12 105:15 105:18,20 106:10 116:15 127:17 192:5 192:11,11 193:7 228:3,3 232:8 247:23 256:10 347:19 347:21 449:23 459:18
relates 36:13 340:8 342:10 348:21 376:9 378:22 380:11 454:16
relating 17:6 59:17 107:3 153:6 155:23

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 506 of 524

347:16 348:20 379:18 441:7
relation 53:13
relationship 239:25 422:17 424:2
relative 24:24 144:11 461:15 461:17
relatively 150:23
relaxed 317:19
release 165:21 234:14
relevance 45:13 142:14 168:17
relevant 20:12 198:16 199:6 200:18 234:23 236:5,8,9 245:18 267:21 278:13 280:11 303:16 319:13 418:25 419:2,5
reliable 86:20 256:4,24,25 257:10
relied 49:21 56:11 63:11 208:8 287:20 287:21 290:6,8 297:24 298:14 338:14 374:8 374:11 385:15 386:17
rely 29:3 30:21 50:1 175:1 209:11 267:6 298:1 310:25 323:17 332:24 340:15 385:10 399:10
relying 29:11 311:11 333:5 338:19,23 339:5 378:4 381:16
remains 266:25
remember 13:4 13:6,20 52:11 107:19 235:8 236:18,23 240:5 275:2 291:15,19 292:21 293:2,6 332:7 436:11
remind 14:8
remission 147:3
removal 97:8,9 97:11,12
remove 73:11 166:15
removed 96:18 96:24 100:11 103:6
render 180:20 215:8 284:16 303:8 451:25
rendered 450:12
rendering 220:4 302:24
repeat 102:6 182:4 268:13 310:16
repeatedly 107:24
repetitive 111:22 112:3 113:8,9,10 118:10
repetitively 107:6 108:4 114:10 115:19
rephrase 30:24 31:1 55:22 84:23 105:22 304:7
replaced 96:24
report 12:2,21 13:12 28:9,11 39:16,18,20,24 40:5,8 42:5 43:15 55:3,8 56:11 59:13 62:3,4,8,13,16 62:21 63:17 141:4,5,19 142:7 143:18 173:23 214:4 214:10 231:11 242:19,20 250:22 251:12 253:4 269:16 269:23 318:9 344:20 349:6 349:25 371:6,8 375:5 382:5 385:23 410:8 417:13,16 435:21 437:1 437:15,24 438:12,22 440:3,3,9,12 441:14,24,24 442:9,12,12 443:5 445:23 446:4 447:16 447:19,25 449:18,24 452:12,19 453:5,9 455:1 455:3,6,13 456:15 457:4 457:20 458:5
reported 1:22 245:15 281:10 326:10
reporter 2:9,10 10:12 14:1,8 15:16,18 79:10 128:22 207:9 208:2 461:2,2 461:22,23,23
REPORTER'S 7:9
reporting 410:11
reports 256:14
represent 11:10 19:21 61:13,16 428:16
represented 168:23
representing 18:8
reproduce 143:8
reproduced 402:14,16,19
REQUEST 8:8
require 33:5 56:25 76:20 138:5 140:8 151:23 187:12 361:24
required 34:4 273:21,25 395:2 398:19 421:18 424:4 441:23
requirement 299:10
requirements 170:5 183:13 183:16,18 190:25 202:5 205:3
requires 169:3 175:8 410:25
rescue 191:12
research 64:21 69:24 71:14 73:2 74:1,6,7 77:25 130:3 175:22 197:22 415:25 416:17 417:18
reserve 313:8
reserved 223:22
residence 99:3 99:18 234:11
residency 65:20 66:7,14,20,24 128:16,18 129:2
resident 66:10 66:13 72:18 73:8 129:6,19 130:9
residents 73:8 130:9
resides 87:24 99:9
resolve 395:24 396:2
resounding 264:19
respect 32:10 48:24 49:3,7 49:11,16 118:8
respond 146:15 146:22 152:3
RESPONDENT 3:14
response 130:14 131:1 146:13 151:4,6 458:9 458:14,17
responses 146:8 146:11 151:1
responsibilities 69:10
responsible 13:19 176:4
restate 35:16 89:20 304:7
restaurant 158:23
restrictions 282:10
result 135:13 143:8 144:23 165:20 220:12 232:22 241:9 264:22 367:14 402:14,17,20
resulted 241:19 363:20
resulting 376:14 378:12 387:12
results 153:23 154:25 155:13

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 507 of 524

156:8,18,19,21
156:22 157:10
159:4 171:12
232:24 238:19
239:8 241:7
244:23 246:7
246:16,18,18
246:22 266:4
274:6 278:8
381:17 382:4,8
382:22 383:4
384:11 392:2
394:4,14
retina 67:13
76:12,18,20
77:1 78:5,10
78:17,17,18,20
78:23 79:3
80:13 87:15,24
88:17,17,20
92:16 111:6
120:11,12
171:8
retinal 10:6
36:18,19 37:13
74:22 76:10
77:11 78:12
87:17,22,25
88:14,14,22
89:4,18,19,25
90:7,8 91:10
91:19,20,21
93:5,6 94:12
94:15 96:11
98:11 111:23
112:23 115:23
120:8 188:15
188:16,18
191:6 206:13
retinitis 405:7
retinopathy
36:17,17
147:13
retrieve 435:6
returned 68:15
reveal 58:17
65:10
revealed 297:2
reversibility
91:7
reversible 90:20
91:1 92:21
review 24:3,8
25:11,12 28:5
50:22 107:16
125:6 127:16
128:2 158:12
159:3,9,11
196:12 209:12
213:16 234:21
235:3,10,20,24
236:1 240:19
240:22 242:18
246:14,24
275:23 329:7
344:2 357:18
360:6,11
368:11 371:22
381:25 386:3
397:10 436:25
440:16 462:9
reviewed 20:6,7
20:11 27:9,25
28:10,13 47:20
52:15 139:17
195:19 208:25
209:4,5 292:1
292:4 360:15
369:23 381:21
385:10 386:17
420:3 434:21
435:21 436:22
reviewer 159:15
reviewing
194:10 195:14
291:22 361:9
reviews 21:7
revise 350:3
389:5,15
revising 349:24
rhodopsin 88:5
88:7,8
Richardson 1:16
2:6 3:4 10:8
17:10,12,14,19
18:2,7,16 21:4
22:12 23:7
25:9 29:19
30:3 437:22
438:10,21
riddled 86:10
right 10:15 12:6
12:13 15:23
16:3 17:21
22:24 24:6
28:17 29:4,8
30:23 31:6
32:17 33:5
35:7 37:10,13
39:9,17 40:12
46:17 47:22
48:16,21,25
49:4,8,12,16
50:11 51:11,22
52:3,5,9,16
53:23 54:6,10
57:10 60:7,13
60:16,17,19
61:21 62:5,17
62:24 63:5
68:4,7 72:24
74:4,8,17 79:6
80:6 81:9 82:6
82:22 84:4
86:23 93:16
94:15 98:13
101:17 102:12
103:7 108:9,22
109:11,14
110:8 111:23
112:22 116:25
118:11 121:15
122:6,7 123:6
124:7,11
125:20 127:7
129:12,25
131:18 132:4
132:13,20
133:5 134:13
136:11 137:15
139:8 143:2
146:6 149:15
149:16 156:9
157:14 160:16
160:19 161:22
163:25 165:1,5
165:8 166:7,25
167:12 168:3
170:1,15 175:2
175:24 176:11
178:1 185:25
186:14 189:12
191:24 192:16
192:22 193:3
193:21 194:8
197:11 199:11
199:16 205:4
208:4,22
210:13,18
211:14 212:10
215:19 219:1
221:18 222:16
222:24 226:6
226:13 227:2
228:15 229:1
229:10,15
230:5,9,14,21
231:18,19
232:12 233:10
234:23 235:23
236:5 237:9,17
238:11 241:6
242:4 243:9,13
244:19 245:24
246:3,16 250:7
251:17 252:17
252:18 254:17
254:24 255:15
255:17 258:5
259:11 260:2,6
263:8,18
264:11 265:13
267:8 268:7,24
270:12,21
271:2,6,14
272:8,17,21
273:2,9,17,22
274:2,8 275:1
275:20 277:7
277:16 278:4,5
278:17 279:11
280:6,13,21
281:2,21 282:7
282:23 285:17
286:20,25
291:5 294:16
296:23 299:6
300:8,12,17,25
301:4,25 302:7
304:4,12,19
306:9,16,20
307:22 308:2
308:14,23
309:6,13 310:6
310:23 311:4
311:12,18,25
313:7,8,20
314:13,22
315:14 316:4,8
317:9 318:3,3
318:9,13,21
319:7,14,15
320:11,13,22
321:7,8,16
322:19,23
323:10,19
324:17 325:14
325:25 326:6
327:10 329:12
331:12,18
332:2 333:6,24
334:2,11,22
335:4 336:5,6
336:18,23
337:12 338:6
339:9,25
340:13,16,17
340:19,20
341:3,4,9
342:14,15,18

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 508 of 524

342:19,24 343:13 344:8 345:2,12 346:3 350:25 351:18 351:19,21 352:2,6,16,25 353:5,9,14 354:10 355:9 356:6,7,10 357:17,22 358:4,12 359:3 359:21 361:16 363:5 364:13 364:19,25 365:9 367:1 368:16 370:17 371:7 372:2,21 373:14,18 374:5 375:3,9 375:11 376:2,9 376:16,23 377:10,20 378:5,15,20 379:5,9,23 380:8,12,13,18 381:18 382:16 382:20 383:10 383:16 385:11 385:20 386:4 387:15,16 388:9,10,15 389:1 390:11 392:18 393:5 394:9,17 396:20 399:15 399:20 400:2,9 400:24 401:12 403:9,24 404:1 405:3 406:25 408:8,12,19 409:6,13 410:9 410:19 411:25 412:9 413:21 414:2,17 415:14,16 417:21 418:11 420:3,8 422:3 423:15 424:18 424:19,24 425:16,24 426:23 428:22 430:2,20 431:4 432:2,6,10,23 434:9,23 435:3 436:16 437:11 437:12,17 438:13,17 440:4 441:5,9 442:22 443:8 447:2,6,8 448:4,9 450:20 451:17 452:4 452:23 453:18 453:23 454:18 454:24 455:4 457:22 458:17 460:11

right-hand 133:24

rigorously 141:7

ring 434:16

rip-roaring 405:6

risk 184:10 371:11 372:19 373:8 374:3,25

risks 151:20

RMR 1:22

Robert 50:2 54:5

role 231:15,20

roles 206:20,23 231:25 232:1,2

rolls 147:22

roman 211:25 448:13

room 13:5 14:17 15:17 138:14 142:18 163:9 169:7 176:11 176:13 208:1 310:6

Rosenfeld 252:21

rotating 66:3

Rounds 23:24

route 117:25 170:22 357:10 358:7,10

routine 161:9 307:16

routinely 130:22

row 411:22

rules 13:25 14:19 462:15

run 268:10

S

S 3:16 6:2 7:2 226:10,10,10 412:5,5,5

sacrificed 91:6

safe 107:25 108:1 110:7,16 111:18 119:23 121:15 122:5,8 122:10,13,19 123:2,6 139:7 140:2,15 141:25 147:15 147:23 155:5 172:23 174:20 175:23 220:20 295:23

safely 140:3 173:16

safeties 81:18

safety 81:24 110:24 111:8 112:2 120:9,20 121:3,5,25 122:2,25 134:23 142:18 148:7,10,22 150:2 151:7 156:21 173:25 175:5,7 181:24 186:8 238:13 258:14 263:15 264:9 265:4 266:15 391:19 392:16 393:3 394:7,22,25 396:20 397:23 398:7 407:9 413:25 414:7 414:12,25 415:18 416:1 418:6,18

Sakarya 6:18 124:23

saline 172:4

San 3:8

saw 174:17 179:11 326:13 354:11 362:3 363:19

saying 37:4 55:7 55:12 73:22 94:9 109:15,24 136:14 142:13 143:1 158:20 196:4 235:13 281:18 285:12 314:8 337:5 373:23 376:25 384:17 386:2 398:2 421:8 440:20

says 51:11 53:2 60:6,15,18 61:8,16,17,21 84:25 110:19 113:10 114:13 129:8 131:23 132:16 133:25 143:21 149:7 219:3 243:16 278:1 279:24 281:11 325:23 339:19 340:13 340:15 350:6 373:7 388:11 399:24 413:4 424:11 430:5 455:11

Scamborova 4:2 10:1

scene 150:24

schedule 143:24

schedules 83:4 83:17 86:22 115:12 116:16 149:2

school 22:4 64:4 64:8,10,17,18 64:19,22,23 65:2,16 66:11

science 83:22 90:4 166:21 169:19 184:24 315:22

sciences 198:2 202:24

scientific 89:22 112:13 189:5

scientist 175:2

scope 32:13 173:22 210:25 211:22 222:11 321:6 322:17 323:7 330:2 448:14 449:3 449:18

screamed 223:14

screen 436:20,25

screened 181:6

search 36:4 37:21 39:7 155:22 369:6 435:10,10

searched 38:3,8 38:15,21 39:2 437:20 438:9

searching 35:7 35:20,21,22 37:20 261:12 368:15

sec 119:16

second 107:14

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 509 of 524

113:8 121:20 133:23 173:19 207:25 222:19 262:20 278:23 280:17 306:11 332:8 343:11 400:4 434:18
secondary 211:3 214:14 215:9 448:17
seconds 44:18 310:10
section 42:22 48:14 57:14 109:4 211:25 212:2,3,19 213:22 214:13 248:6,23 250:3 399:7,11 417:14 430:24 447:25 449:13 449:22 450:4,5 450:21,23 451:9 452:18 455:7 456:4,14
sections 450:17 452:18
sediment 184:12
see 11:24 14:9 25:10 34:15 35:5 36:2 37:5 40:19,22 42:9 42:25 48:7 60:20 67:14 70:5 71:7 76:16 77:14 79:1 82:11 83:12 85:18 87:13,19 89:2 92:23 98:7 106:6 113:2,5 113:9,14,24 133:23 144:21 146:2 151:14 154:5 158:1,2 161:10,17 175:19 195:1 195:20 209:20 210:4 211:6 212:3,24 213:1 214:16 217:24 218:18 219:8 224:7,24 231:4 231:9 232:11 232:25 235:4 235:10,21,23 239:16 240:8 241:14 242:22 245:17 249:5 253:24 254:13 255:8 257:17 259:5 261:17 262:8 269:23 270:3,18 274:15 278:10 285:16 302:3 305:12 308:10 313:25 315:1 319:4 322:9 335:21 339:18 344:19 349:21 350:3 351:5,12 354:3 368:21 369:4 370:4,5 370:11,14,20 371:14 373:6 373:11 379:15 383:2 389:12 391:13 392:6 395:18,18 397:12 404:11 413:2,4,13 414:11 419:12 421:5 434:17 448:20 450:5
seeing 258:21 308:8
seek 224:5 367:11
seeking 249:17 425:21
seen 40:12 63:9 135:14 161:25 209:6
segments 449:23
select 297:20 304:19 332:14 334:11 443:19 444:4
selected 261:21 330:21 352:24 355:1 361:2,4 365:4 367:18 368:2 395:14 462:11
selecting 403:23
selection 116:19 261:2
selective 136:24
send 41:19
sense 29:2 41:8 75:14 209:10 214:23 229:5 289:11
sensitive 242:8,9
sent 435:23,25 436:8
sentence 85:1 88:25 106:8 113:14 134:3 222:19 223:5 303:16 329:25 337:19 338:16 345:5 373:6 376:9 389:16 392:12,25 400:15 412:18 413:8,13
separate 380:17
separately 386:2 390:15
September 18:23 25:1 41:25 47:10 52:20 53:2 60:19 61:4,19 291:13 372:5
sequence 359:1
serious 318:5
served 284:4
session 5:10,11 411:21
sessions 23:2
set 34:20 198:22 199:1,22 200:12,25 201:8 202:12 215:24 250:8 461:12
sets 107:19
setting 50:15,18 73:25
settled 12:23 433:5
settlement 13:1
settling 180:12
seven 16:22 65:22 446:7
severe 188:15
sex 149:4
shake 313:25
share 436:19,25
shared 25:8
sheet 462:12 463:18 464:1
shelf 172:10 190:24 295:4
shift 138:22
shipping 179:2
short 104:7 123:25
short-circuit 194:13 451:8
shorter 167:6
shortly 25:3,5 372:22
shortsighted 166:21
show 61:15 115:3,18 261:9 264:7 266:13 272:25 332:15 383:24 392:14 393:1 394:21 396:19 397:21
showed 105:24 214:21 260:8 263:13 264:3 266:6 374:12 379:19 393:22 413:19
showing 156:8 267:7 268:16 372:18 394:4,7 394:14 398:6 406:23
shown 60:22,23 61:1,7 115:8 115:21 266:25
shows 139:4 332:11 334:5 396:13
shut 191:7
shutting 160:2
shy 225:24
sic 164:13
side 77:1 148:12 163:8
sign 41:15 462:8 462:9
signal 112:2 297:1
signals 362:12
signature 41:12 41:16,17,25 462:7,13 463:6 463:23
signed 18:22 21:15,16,20 24:25 25:17 26:4,9 27:19 42:5 43:15 46:16,20,25 47:4 51:22 53:18 58:25 62:3,4 63:4,8 209:1,4 291:25 434:23 436:9 462:12
significant 134:7

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 510 of 524

397:4 398:14
signing 21:25 58:13,24 62:8 62:12 438:22 439:13 462:11
similar 82:20 85:15 197:17 198:2 202:25 278:2 283:4 393:15 417:8
similarly 450:16
simple 354:6
simpler 93:1 155:25 204:3 258:17 329:4 374:21 382:12 423:18
simplest 87:9
simply 21:24 30:6 56:23 180:12 428:20
Sincerely 462:18
single 59:13 104:17,19 107:18,24 108:3,6,17 109:6 110:21 111:20 112:1 119:17 130:23 134:25 141:10 145:13 157:20 261:11 271:2 273:7 274:7 277:13 278:3 285:3,4 374:15 385:5
sit 13:5 163:8
sites 234:9,10 244:14
sitting 16:22 21:17 27:18 44:5 213:25 360:18 382:3 386:20 397:18
six 18:24 19:13 71:9 102:1 133:25 134:6 248:15
six-pack 101:24
six-packs 102:2
size 100:17 149:1 189:4 420:17 421:22 421:25 424:1
skill 19:22 34:5 35:3 36:21 57:12,19,24 58:4 67:22 68:2 143:15 196:24 197:13 198:10,14 199:9,15,21 200:8,13,17,22 201:7,23 202:5 202:13,18 203:8,13 204:6 204:9,19 205:8 205:23 211:1 212:8 223:20 285:6 288:4 299:18 303:23 331:4 337:21 339:16 340:7 342:3 343:7 344:23 345:1 345:16 346:18 347:14 348:4 348:19 358:25 359:4 364:4 366:22 381:6 383:13 386:13 395:12,13 404:11 405:11 440:13 446:3 448:15 454:8 456:8
skilled 116:4 119:8 133:1 134:10 144:4 153:24 157:12 159:20 162:15 191:23 193:18 195:10 196:17 197:8 219:10 221:3 222:2 224:23 237:3 247:25 248:11 248:13 249:16 259:9 263:4 294:5,18 295:8 296:2,5 304:18 311:1 316:12 316:12,15 352:24 369:17 369:25 370:23 373:15,17 377:7 399:13 400:8 425:13 425:20 431:8 432:1
skills 200:25 201:6,9,11
skin 92:6,7,8 118:2 170:1,13 171:22
skip 87:8
sliced 166:16
slight 179:14
slightly 39:25 225:5
small 366:9
smaller 104:1,3 158:6 190:2 313:6 364:12 364:19 367:24
smallest 190:21
societies 75:13 75:22
sole 374:10 379:17 409:23
soluble 420:1,8 420:11 425:8 425:15,23
solute 180:2
solution 172:5 180:1 181:25 184:1,4 309:18
solutions 184:20
solvent 180:2
somebody 78:9 299:19 326:21
someone's 92:7 137:11 184:1
son-in-law 163:6
Song 3:18 9:23 314:3
sorry 12:5 20:17 26:1,24 27:25 32:20 44:23 47:19 53:13 60:10,23 65:9 71:10 76:22 87:7 88:6 90:12 94:6 101:6 104:5 105:17 108:19 109:17 110:2,5 113:8 118:6 119:15 140:5 151:10 188:7 193:23 205:17 211:19 229:17 231:12 232:15 233:3 246:2 247:2,16 250:8 252:3 259:4 272:7,13 274:25 275:10 275:17 281:6 281:15 295:13 306:10 307:10 307:24 310:7 310:13 314:3,4 315:20 327:5 334:2 335:12 336:8 337:4 338:5 339:2 340:9,12 343:14 349:1 355:12 361:6 362:21 363:4 384:10 390:24 392:24 408:21 413:11 418:14 425:10 428:10 434:17 455:22 455:23 456:18
sort 64:20 80:25 83:13 112:1 211:12,19 300:23 376:19 409:11 421:20 422:10
sorts 174:4 410:13
sought 262:2 334:17
sound 52:3 68:4 312:21
sounds 20:21 126:7 217:8 223:24 313:7 423:19
source 155:3,8
sources 154:11
South 253:5
space 96:23 97:1 103:7 192:7
speak 51:9 459:16
speaking 30:14 101:20 161:4 177:11 185:22 185:23 190:6 236:15 430:8
special 64:7 139:25
specialist 75:11 75:21 76:2 78:5,12 79:3,4 206:14
specialists 75:16 78:8
specialization 66:14,22 73:9 78:25 130:10
specializations 75:9
specialize 64:9 64:13 66:2,12

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 511 of 524

66:19 67:7
specialized 67:12 68:10 131:4
specialty 67:11 75:8 76:4 78:11
species 86:11 101:16 102:24 116:16
specific 52:24 90:22 94:21 105:9 116:17 139:18 162:3 173:9 223:9 242:13,14 258:9 263:23 265:23 294:1 302:24 320:19 336:21 345:15 351:24 357:7 365:2 401:16 410:24 426:7 427:3
specifically 44:21 47:15 50:21 235:9,25 274:16 339:11 339:11 349:17 350:6,7,22 351:4 381:24 385:18 428:9 457:8
specifics 172:7 172:16 241:12 294:9 368:11 409:25 442:5
specified 101:5 144:25 189:23 229:4 331:2 337:24
specifies 321:19
specify 386:25 429:7
spectrum 71:18
speculating 122:2 215:15 325:18
speculation 94:17 104:15 115:1 116:11 117:2 119:12 120:24 121:22 122:16 123:9 126:21 133:7 134:15 137:17 138:10 139:12 140:23 147:20 159:7,24 165:11 169:17 170:8,17 172:1 173:22 180:7 180:25 182:3 190:4 193:14 209:14 236:7 242:6 259:13 260:14 325:16 373:20 403:16 417:2
speculative 116:12 158:24 348:22
spend 265:11 395:10
spent 64:18
spike 421:4
spikes 367:20
spoke 25:2 52:8 53:1 195:16
spoken 24:16 135:10
sponsor 410:8 411:3
sport 313:2
sprouting 231:25
Square 1:17 2:6 9:12
squeeze 23:1
stability 172:10 181:13,15 232:1
stable 190:24 349:13 350:18
stain 426:14
stand 229:24 396:9,16 442:8 457:19 458:8 459:9 460:1
standard 73:15 78:2 93:8,10 108:11 127:22 211:8,14 253:2 292:10 415:7 422:7
standardized 257:9
standards 142:18 209:20 307:4 447:10 448:1
star 158:23
staring 297:18
start 14:5 69:20 102:16 114:4 145:9,9 151:12 151:13 211:22 219:13 234:1 238:4 272:20 317:2 325:22 326:5 332:12 334:9 390:10 409:20 455:5
started 26:13 33:3,7 151:11 167:25 224:3 285:13,22 286:8 335:1 361:10
starting 33:6 100:19,20,21 318:23 365:23 366:17,18 368:2
starts 359:18 447:24
state 11:1 76:1 96:11,16 97:5 98:9 223:14 231:2 266:18 372:16 391:25 394:25 429:21 448:10 461:3
stated 320:5 338:16 362:22
statement 88:24 90:23 121:14 128:22 130:20 131:11 162:9 167:20 195:2 205:22,22 308:13 349:25 351:14 374:8 374:24 375:17 375:18,21,24 383:15,19 385:21 389:6 394:12,20 395:20 396:9 407:11 408:15 418:23
statements 42:15,17,19,20 62:16 389:25 390:1
states 1:1 42:13 42:23 47:1,3,3 51:7 60:25 78:8 186:19 410:24
stature 104:7
stay 43:22 161:12 295:3 310:9 456:13
Stenographer 10:14,22 13:23 403:13
stenographica... 461:11
step 34:1 198:19 326:16,20 332:8
step-by-step 33:22
sterile 152:17 177:18,19 178:5
sterilely 295:6
sterility 172:11 267:14
sterilization 152:18
Stewart 245:8,9 245:12,24 246:10,14,22 275:23 276:18 277:5 280:6,7 280:16 281:19 378:1,22 379:11 380:6 381:18 382:4 382:25 383:1 384:16 385:19 386:17 388:11 390:11,12 393:21
Stewart's 246:6 386:8,10
stick 150:10 342:8 450:2
sticker 31:10
sticking 112:21
stipulates 45:23
STIPULATIO... 8:13
stock 187:20
stocking 187:17
stop 95:9
stopped 335:3,4
stopping 95:5 225:25
store 295:17
stored 295:20
straightforward 442:2
strategy 84:17
stream 155:8 160:3
Street 1:23 463:2

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 512 of 524

strength 154:15
strengths 154:14
strike 31:3 54:3 90:2 93:2 103:24 109:18 110:1,5 114:20 114:22 126:3 209:15 221:4 253:20 255:11 257:20,24 277:24 291:21 317:25 349:3 387:5 391:20 391:22 414:23 432:17
strikes 223:11
strong 75:11 122:17 171:4 220:18 266:8 295:12
structure 88:18 98:16 342:3
structured 341:17 450:22
struggling 162:17 202:16
studied 33:17 74:14,18 104:2 105:8 120:17 127:8 129:8,13 252:22 282:11 283:11 388:18 388:19 414:10
studies 82:18,20 85:8 86:4,18 87:1,2 106:1 115:8,11 127:17 152:4 153:5,7 154:21 155:1,7 156:9 157:19 173:25 174:2,4,10 175:3,12,16 254:5,6 256:10 267:5,6,9 372:24 381:13 381:16,17 384:21 385:4 385:12 386:24 393:22 402:8 417:4,9
study 80:8,14 82:3 84:1 85:12,14,20,25 87:5 89:8,9 91:4,13 92:13 94:1,4 96:10 98:4,7,10 99:11,25 100:9 105:24 107:1 107:10 108:5 108:16,22 109:6,20 110:7 110:15,19,20 111:3,12,14,21 112:5,16 115:3 115:18 116:1,2 118:9 119:17 120:14 123:11 123:12 125:17 125:19 131:25 153:23 155:11 155:13,17 156:2,14,15,16 157:9 158:4,6 158:8 241:12 254:7 255:19 256:14 258:10 258:11 264:15 264:18 266:12 266:23 268:19 269:18 270:2 271:11 272:17 275:4 279:3,5 280:18,24 281:3,7,9,24 284:19 360:4 380:16,17 388:21 391:19 391:25 392:5 394:13 396:5,6 397:9,25 408:18 410:3,8 412:23 413:18 414:24 415:4 415:17
studying 22:4 49:24 64:20 96:10 112:7 114:11 120:7 120:10 164:2
stuff 147:23 253:9
sub-isoforms 238:25
subcutaneous 170:24 172:22 173:14 183:19 424:15 429:5
subcutaneously 171:22 173:11
subgroup 281:12
subgroups 284:24
subhead 451:19
subheading 451:10,18,20
subject 73:2 111:12 112:25 130:3 159:13 185:13 457:24
subjected 135:2
submit 12:21
submitted 12:1 12:25 13:12,13
subsection 212:7
subsequent 73:9 130:10 131:6 139:5 143:11
subsequently 66:21 141:15 153:1 175:14 405:16
subset 177:11,13
subsidiary 321:17
subspecialties 74:21 75:2
subspecialty 74:24 75:5 78:23
substance 58:18 289:18 306:25
substances 98:22
substantial 19:6 43:11 69:24 168:23 364:1
substantially 56:8
substituting 347:1
subsumed 59:18
succeed 166:24
success 19:23 152:5 166:20 216:4,7,13,17 216:21,25 219:7 221:6,9 221:16 262:13 264:19 285:8 412:21 451:1 451:12 456:10
successful 189:1 189:7 285:9 364:6 366:23
suddenly 142:10 144:17 216:17
Suffice 216:24 317:4
sufficient 303:8 433:15 434:4
suggest 123:24 152:4 217:22 329:23 365:18 371:5 379:25 388:12,17 389:2 444:12 444:15
suggested 286:3
suggesting 55:2 115:25 141:24 325:11
suggestion 136:8
suggests 46:24
suitable 34:12 34:13 427:18 428:4,18
Suite 1:23 3:7 463:2
sum 23:19 403:8
summaries 159:21
summarize 159:5
summarized 106:7
summarizing 142:1
summary 48:8 48:15,17 87:11 218:17 245:25 246:6,7 248:5 248:25 386:9
summer 9:24
suntan 118:2 215:4
Sup 107:2
super 171:3
superb 158:17
superior 274:6 395:7
support 8:1 136:16,19 263:18,21 310:25 327:22 399:12
supported 371:11 373:7 374:3,25
supporting 87:25 265:14
supportive 333:12,13
supports 155:4
suppose 387:3 435:23
supposed 14:19
supposition

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 513 of 524

133:19
sure 14:8 22:6 25:25 35:18 40:11 61:25 73:21 75:17 91:24 95:14 102:8 110:18 124:4 125:11 126:11 130:15 141:13 145:8 149:13 150:6 150:13 152:21 173:20 177:16 177:23 179:15 192:24 196:6 197:1 223:17 226:3 234:6 262:25 268:14 276:22 288:2 290:10 301:1 306:14 310:17 343:14 361:8 370:9 374:18 390:7 420:9 421:24 428:23 433:7,20 435:4 436:6 437:10 446:17 452:2 457:10
surface 136:23
surfaced 214:20
surgeon 43:25 78:6 130:25 132:2 169:20 206:17
surgeons 131:5
surgeries 70:11
surgery 68:10 70:10,13,16 71:13,14,23 72:5,9,17,21 73:4,7,10,12 73:14 74:1,5 74:12,17 76:9 76:15,20,24 77:12,19 97:9 100:7 103:19 108:13 126:19 127:3,7,24 128:9,12,14,19 128:24 129:2 129:12,17,22 130:6,9,11,18 131:3,8,10 133:5 135:1 139:16,20 426:13
surgical 58:6 67:13 77:21 78:16,20 96:11 96:16 97:5 98:8 107:7 142:22
surgically 106:2
surrounding 36:25
suspect 63:18 401:13
sustain 115:22
sustained 374:18
SW 3:19
swayed 326:22
swear 10:13,17
switched 265:6
sworn 10:25 15:19 461:6
syringe 100:16 176:14,18,20 178:10,12 181:5 189:21 256:1 296:14 297:18 298:9 298:16,18,23
syringes 141:16 297:17 298:12
system 435:16
systemic 97:25 260:22
systems 86:12 435:5

T

T 6:2 7:2 226:10
table 50:10,13 50:17,19 211:21 240:5 245:5,15 250:22 278:21 278:22,22,24 370:5 380:24 397:11 447:23 449:9,11 450:3 450:16
tables 360:1,5,5 360:9
take 23:22 24:21 33:22 46:7 51:5 61:14 63:15 65:25 70:1 77:11 79:6 95:4,18 111:5 115:7 119:7,9 123:21 123:25 124:3 125:5 138:20 145:12 149:6,8 156:25 188:22 190:8 198:18 207:15,21 226:2 239:19 241:3 244:10 249:3,4 270:5 276:16 285:18 304:22 316:15 317:16 329:16 332:5 337:22 347:24 368:4 380:22 388:16 389:8 390:21 391:9 393:11 396:25 405:10 405:12 411:17 411:19 431:20 447:22 448:5 453:15 456:17 456:22
taken 124:9 167:25 206:22 226:8 266:7 306:18 307:15 412:2 446:25 461:11
takes 61:3 224:25 234:4 251:22
Talamo 6:9 95:22 96:13
talk 13:24 14:3 29:24 41:5 63:16 226:17 236:22 250:11 262:6 382:19 388:4 390:6 403:14 450:1
talked 67:19 122:3 250:7,9 260:4 390:4,4 401:14
talking 21:14,15 31:12,19,22 37:15 41:6 57:23,25 58:3 68:1 91:17 102:17 108:7 108:23 118:10 122:8 123:10 137:5 140:6 149:14,20 151:6 160:15 170:21,21,22 171:19 173:24 174:14 184:5,9 184:10 208:17 234:1 272:20 275:17,24 279:3 312:12 324:11 334:7 343:17 351:24 352:17,19 357:24 379:4,7 380:6,15 409:20
tar 296:11
target 175:13 189:2 222:3 297:20 298:15 298:21 299:14 304:3,10 320:5 320:10 323:25 333:16,16 354:23 356:2 362:9,10,15 363:8 365:2 431:13 443:22 451:5
targeted 189:3 319:17
targeting 311:8 413:7
targets 294:1
taught 219:17 220:1,23,25 224:17 294:1 297:12 298:5 301:8,19,20,20 323:13 324:2,5 329:19 331:1 349:13,14 350:18 367:11
teach 222:21 223:3 327:19 363:5 454:7
teaches 221:21 221:24 225:21 296:17 301:25 303:15 304:3 304:10 320:14 320:17 321:24 328:10 329:5 330:19,25 335:24 362:25 363:6 453:21
teaching 217:13 223:7,8,18,21 285:23 286:9 297:13 302:20 302:23 321:20 329:19 338:15 361:19 362:14 365:15,17

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 514 of 524

teachings 365:3 454:15 456:6
team 20:9,9,18 20:24,25 21:9 23:7 54:22 55:1,7 57:7,9 57:10,23 197:15 198:12 198:15 200:15 200:19,24 201:16 202:4 203:9,12,15 205:1,12,20,24 206:1,6,15,25 288:5,8 313:2 314:1 354:24 426:2
teamwork 288:14 293:15
tear 120:15 122:22
technical 234:21
technically 39:19,19,25 75:15
technique 177:20,23
tell 15:8 146:3 146:14 160:23 161:15 178:25 195:8 229:20 253:10 280:4 280:25 287:4 293:9,11 294:3 294:4 301:3 313:11,12 344:20 369:24 440:19 443:18
telling 61:8,16 196:14 378:18 379:2
tempted 347:24
ten 23:21,21,24 163:10 446:16
tens 261:25
term 111:15 117:4 144:11 175:8 181:12 214:23 223:22 348:15
termed 427:7
terms 75:25 104:18 165:22 193:19,23 195:16,16 209:3 233:19 285:4 296:23 298:25 384:6 442:8
terrain 205:16
terrified 163:4 260:21
terror 261:22
tested 240:14,16 240:20 241:4 415:12
testified 11:2 28:14 47:22 52:14,19 54:2 61:9 292:16 309:9 428:2 432:19 434:19 458:16
testify 16:15 428:17 461:7
testifying 335:15
testimony 10:18 15:18 17:5 20:5 28:21 36:9 47:21 51:24 55:11 56:15 60:1 101:10 120:4 124:17 136:13 142:4 143:4 147:19 200:21 201:3 205:14 221:2 256:22 258:7 259:14 285:21 289:6 299:3 302:2 303:12 304:6 306:25 313:14 323:22 324:19 327:25 329:10 329:14 333:8 335:20 344:10 345:19 367:7 368:25 374:1 375:5 376:4 386:6 389:24 428:12,14 441:3,18 444:7 458:9 459:9 460:1 461:10
testing 257:9
tests 151:18 169:5
text 276:17
thank 10:22 79:19 125:14 164:15 247:18 277:1 430:14 446:21 460:7,9
themes 25:7 289:14 293:13 293:16 437:14 440:15 441:21 442:25 443:5,7
theoretically 98:2
therapeutic 81:8 134:22 198:5 203:3
therapies 262:3
therapy 72:13 74:15 78:6 82:19 85:10 96:21 107:4,6 108:18 110:12 123:15 129:9 130:20 135:11 135:19,20 139:2,3,15,22 146:16,22 148:6 149:22 152:1 153:13 164:4 171:10 250:16 252:12 252:13 253:10 253:16 261:5 341:19,22,24 364:7
they'd 294:19,20 294:21
thick 328:17
thickness 120:16 279:23
thin 328:17
thing 37:5 39:24 54:10 56:13,17 65:11 119:22 120:17 142:21 153:15 154:2 180:20 192:2 195:22 230:9 248:18 258:4 264:2,4 316:2 316:6 402:4 410:25 440:20
things 11:23 19:4 22:5 33:15 36:4 38:3,12,14,20 39:1,8 78:21 83:8,17 84:12 88:20 92:10 96:20 111:11 114:11 143:14 152:15 165:13 172:11 178:3 190:9 194:19 194:22 197:6 218:12 223:19 226:24 232:6 254:7 265:1,17 265:20 279:7 283:10 286:19 300:6 328:21 328:24 340:19 344:13,17 348:22 410:13 417:7 443:13 445:2 450:25
think 15:1 21:8 23:19 24:23 26:25 37:4 40:2 47:21 51:20 61:23 67:19 78:13,13 78:18 84:8 86:1,15 92:23 92:25 94:8,10 95:20 104:8 108:20 119:21 121:1,3,12 126:7 136:8 137:6 140:5 142:25 149:23 150:23 151:8 153:14,20 157:17 166:3 166:21 169:9 169:18 171:7 172:5 174:8 178:8 189:2 193:22,25 194:14 197:9 207:2,2,17 208:21 212:4 218:17 227:15 231:14 234:7 238:5,6,9 247:6 249:6 250:7 253:2 259:2,4 260:4 261:20 262:19 262:22 269:14 270:1 276:18 281:18 283:20 284:13 290:5 292:13 300:1,5 301:23 303:10 303:20 305:10 311:19 313:22 313:23 314:8 315:12 317:1 320:8 324:20 324:20 327:5 328:3 330:9,10

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 515 of 524

334:6,14 335:15 338:22 340:2,6 343:6 346:13 347:13 349:6 355:23 356:19 358:24 363:9 367:9,23 375:18 377:23 378:1 386:1 387:7 390:3 398:4 401:25 402:22 405:10 407:5 411:20 416:16 417:22 423:17 427:21 431:18,18 434:10 436:5 438:4 441:19 443:3,4 460:5
thinking 22:10 25:7 116:23 241:15 285:3,5
third 107:15,16 212:18 296:8 430:9
thorough 143:10
thought 59:22 59:23,24 62:23 62:24 185:19 214:22 297:4 297:22,24 312:10 373:17 373:22 376:22
thousands 135:8 261:25
thread 324:21
three 62:3,11 107:19 123:14 132:17 135:3,7 138:2 145:20 150:5 161:8 193:7 211:13 220:2,2,10 273:6 274:5 277:12 278:3 295:17 330:17 450:25
time 9:10 10:3,3 11:25 12:4,5,6 14:14,14 15:4 15:4 21:16 22:22 24:21,24 28:8,13 31:17 31:17 43:14 44:3,6 45:19 46:20 47:9 51:21 53:12 61:15 62:8 63:15 64:19 67:20,21 69:14 70:24 80:2 99:4,18 113:20 114:11,15 122:9 123:13 124:6,10,16 131:6 133:2 134:12,13 135:7,21 137:11 146:3 149:24 167:7 176:11,12 197:14 199:6 207:8,16 209:4 217:25 218:2,3 218:4 221:11 223:21 225:15 226:5,12 234:11 246:24 261:1 274:24 274:25 275:13 276:9 279:2,5 279:9,21 282:11 286:1,2 286:3 292:4 294:10 300:11 306:15,19,23 317:15,17,19 337:5 381:24 383:13 386:12 391:4 408:3 411:24 412:8 412:24 436:18 444:13 446:6 446:10,22 447:1 457:24 459:14 460:10 461:11 462:14
time-out 343:10
times 1:17 2:6 9:12 11:15 91:5 132:17 163:11,11 283:17 312:19 321:23 326:13 328:4 338:22 363:10 385:22 401:21,23 404:7 409:18 458:3
timing 54:18,23 161:13
tissue 87:25 88:1 106:12
tissues 112:8,9 112:15,20 115:16 123:16 175:13 231:22 232:10 426:15
title 42:23 48:20 89:12 419:21
titled 48:17
today 9:22 10:20 11:12 14:10,19 16:1,17,23 19:18 21:14,17 21:18 27:18 44:6 161:17 213:25 255:20 360:18 382:3 386:21 432:19 447:8 448:24 452:25 453:8 458:10 459:10
today's 9:9 20:4 40:1 47:21
told 59:22,23 149:23 195:21 195:23 196:9 198:9,16 204:4 288:10 290:20 294:8 299:19 442:14,16 444:3 446:9
tolerance 406:20
tolerate 179:14
tolerated 109:9 110:21 111:2 111:13,17,22 119:20,22 120:6,9,21 121:2,4,13 122:5,12,24 132:18 219:21 224:13 285:25 286:10 325:3 325:13,25 326:5 328:5 374:14 400:1,7 402:21 404:18 404:22 405:2,5 405:10,18,24 406:21,25 407:5 408:16 412:25
tomorrow 223:16 299:22
top 87:11,24 223:13 251:10 379:24
topical 130:16 131:2,14 136:20
total 23:19 403:8
totality 284:25 285:5,18
totally 144:20 158:22 314:24
tough 14:4
tougher 367:22
toxic 83:15 84:2 84:11 88:13 374:19
toxicities 81:19 82:18 105:25 115:13 175:17
toxicity 80:14 81:9 83:6 85:9 87:14 89:13,19 90:9,23 91:21 94:15 96:12 98:11 99:3,8 99:15 100:2,12 106:10 107:20 111:23 115:23 116:1,15 135:14 174:3 371:12 372:19 373:8 374:4 375:1 405:13 416:20,23 417:5
trabecular 97:21 98:12,15
TRADEMARK 1:1
trained 69:25 138:16 169:20 202:11 204:12
trainee 76:8
trainees 16:11
training 65:14 142:19 178:6
transcript 5:2 5:16 28:6 52:16 461:10 462:6,8 463:12
transcription 463:15,19 464:7
transfusion 420:21,22
transient 90:20
transparency 179:4
Trap 19:25 227:2,4,5
traps 231:7
Trask 3:17 9:22
travel 47:16
traveling 47:9

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 516 of 524

treat 69:3,7,13 69:17 160:16 254:3
treated 77:9 139:23,25 140:3 248:16 273:24 277:22 281:13
treating 49:23 69:11,20 80:21 136:3 139:3 175:13 231:3 348:3 364:3 406:4 420:13 440:14
treatment 36:15 49:25 73:5 77:18 130:6 139:19 151:20 152:5 153:6 154:1 160:18 162:25 163:1,2 163:15,21 165:5 168:23 197:19 224:6 226:23 249:21 261:14 279:20
treatments 197:23,25
tremendous 260:24 261:7
trend 395:17
trending 395:22
trends 263:25
trial 1:2 13:2,3 45:22 87:5 141:8 156:11 241:8 244:18 244:23 245:4 245:14,23 246:1,1 260:8 261:15,16 263:22 265:2 269:10,12 276:19 277:6 277:11 282:25 283:1,4,7,9,15 283:19,19 284:17 325:5 326:12,23 377:17 379:10 379:19 380:11 381:2 382:15 384:3 399:19 406:2 407:18 408:2,3,4,7 410:6 415:9,11 415:13 417:10 433:6
trials 50:1 159:5 167:22 171:14 175:15,19 238:19 239:9 239:10 240:13 241:4 283:5 371:10,18,21 372:18 373:7 374:2,24 375:11,13,20 375:22 376:11 378:10,20,23 379:8,12,25 380:5,7,20 381:4,8,19 382:5,7 384:19 387:10 388:7 388:12 400:22 406:15 415:5
tricks 84:18
tricky 417:25
tried 77:22 215:18 217:5 224:18
Trip 79:24
trivializing 157:15
true 42:14,16,18 82:5 148:7 150:19 167:20 202:23 258:4 267:5 330:9,10 351:16 463:14 463:18
trust 143:1,6
truth 10:18,19 10:20 461:7,8 461:8
truthful 43:10 43:12
truthfully 16:16
try 14:3 41:7 95:14 121:11 162:6 197:11 201:20 230:10 258:13 268:10 315:3,24 317:14 364:2 415:22 425:11 435:7,15
trying 37:20 58:11 78:15 84:1,18 92:25 125:10 158:2 164:7,10 165:1 167:11 168:18 199:25 236:18 251:15 259:15 259:21 262:5 316:13 329:22 332:6,21 335:13 338:25 343:2 366:5 389:10 451:20 452:17
trypan 426:16
tube 422:25
turbidity 179:14
Turkey 141:11 142:8,13,15 406:15
turn 32:3 40:15 42:8 48:3 49:18 51:3 82:10,11 106:15 109:3 116:8 209:18 218:16 227:8 231:10 250:10 269:25 304:25 305:8 307:7 311:24 349:4,5 359:13 361:7 369:15 370:13 377:6 384:24 412:12 419:7 429:17 438:11 453:23 455:2
turned 44:18 108:1 224:14
TV 149:8
twelve 277:15 278:25 279:5 280:1,3
twice 51:10
two 18:18 19:13 70:8 71:7,8,11 99:5,10 102:2 104:20 107:18 108:4,24 123:13 133:16 150:5 162:6 175:11 187:5 211:13 218:2,3 219:18 220:10 231:14 234:7,8 234:17 244:13 244:15 246:15 249:4 273:20 274:17 278:23 278:24 292:14 292:22 330:17 348:11 358:15 382:6 392:13 392:25 401:21 403:1 404:16 455:9 457:1
two-year 156:22 246:17 392:1
type 135:24 149:9
typical 43:24,25 253:15 326:12 363:23
typically 43:22 103:13 149:2 151:16,25 156:4 157:11 157:24 159:11 168:2 192:6

U

U 430:6
U.S 1:11 293:7,7
uL 430:5,11
ultimately 12:25 166:7 167:14 175:15 346:12 433:4
umbrella 348:7
unable 319:23
unanswerable 169:11
unaware 93:10 93:12 274:17 356:20
uncertain 296:22
uncomfortable 318:4
undergo 169:5
undergoes 135:1
undergone 103:18
undergraduate 63:21
undermine 264:11
understand 14:22 15:5,9 15:20,25 21:21 29:7 31:5 32:3 32:13 34:9 37:7,20 39:15 39:21,23 43:5 55:20 58:11 67:20 68:7 69:2 73:22 78:15 81:20 86:7 92:24 94:9 98:8 104:16 108:15

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 517 of 524

109:21 110:18 113:3 147:10 160:1 168:16 168:19 196:3 198:13 200:10 201:14 203:5 203:16 204:22 204:22 208:11 210:8 211:12 213:9 216:5,12 216:17 217:4 217:10,12 223:7 251:15 259:16 265:25 268:11 281:16 297:21 302:21 303:5 315:12 315:25 316:14 320:17 324:10 329:24 330:4 332:21 335:14 343:12 348:3 350:14 361:9 361:19 366:5 382:9 390:8 398:1 410:4 433:24 450:8 450:22 452:2 456:3
understanding 19:17,20 41:24 86:22 88:25 109:14 147:7 155:4 181:23 182:7 183:6,12 183:16 211:24 217:14,19,20 220:7 262:12 294:16 307:19 362:6,18 386:11 387:24 388:5
understandings 36:24 383:12
understood 15:12 30:20 78:14 191:24 308:20 314:11 321:4 322:16 323:6 330:1 349:12 429:22 430:16,25 457:6
underwent 106:3,4
undoubtedly 152:7 402:2
unduly 366:2
unfamiliar 138:17
Unfortunately 287:19
unimportant 117:16
uninjectable 180:21
unit 192:7 422:17
United 1:1 42:13 42:23 47:1,3,3 78:8 186:19 410:24
University 16:11 64:6 67:4
unknown 141:11 180:18 181:10 332:18
unliable 355:25
unmarked 39:16
unpack 300:4
unreasonable 365:23
unsafe 148:17 180:21,23 373:18,22
unsigned 436:9
unsuccessful 166:7
untaught 214:23
upper 163:7 297:13 334:18 334:20 355:7 355:10,13,14 355:18,19 417:11 419:22 422:10
uppermost 443:3
urge 135:19
USA 1:4
use 19:25 41:2,7 41:16 72:7,10 100:6 103:19 114:23 117:4 129:5 136:19 137:13 172:23 173:2 174:9 175:23 179:15 179:19 186:25 187:24 188:19 189:20 193:11 194:16 195:10 210:17 214:23 240:23 243:19 243:24 248:19 251:25 252:1 252:11 253:5 254:9 255:18 255:19 267:18 294:5 296:24 298:11 308:17 311:2,20 324:15 327:8 364:12,19 399:14 400:8 421:13 422:2 423:22 425:7 425:14 426:12 431:2,9 443:1 444:13
useful 242:13 417:19
uses 189:25 322:22 360:24 427:22
USP 183:7
usually 65:15,19 156:11,12,13
utility 80:21
utilize 56:22 72:2 86:25,25 143:16 154:11 155:8 171:6 181:5 248:13 249:20 260:24 303:24
utilized 20:12 127:9 226:22

V

v 1:6 3:17 412:5 462:1 463:7 464:2
V.E.1 430:24
vague 30:25 37:22 81:11 82:7 86:5,24 90:10,14,17 91:2 104:14 108:2 116:10 117:1,22 118:19 127:15 138:9 139:9 142:4 144:8 148:8 150:21 158:14 161:23 163:18 168:15 172:3,24 173:8 180:5 181:18 184:2 187:9 189:18 190:3 193:13 195:12 196:21 217:14 222:10 237:25 268:8 282:8,24 301:17 304:20 314:23 316:21 322:25 331:14 332:3,4 335:5 335:19 348:9 358:5 360:22 373:19 414:3 415:3,21 416:24 418:13 424:25 458:18
vaguely 185:10
value 143:7 154:12 386:9
vancomycin 107:4 108:8 109:8,21 119:19
variability 147:8 148:5 150:1 160:23 267:12
variable 83:21 83:21 146:12 151:1,3,5 178:2 234:10
variables 193:25
variation 103:22 148:9
varies 69:7 145:17
various 20:6 21:3 23:6 29:19 84:3 115:16 142:20 151:18 189:12 219:24 232:25 263:25 293:13 304:15 317:12 414:25 426:15 447:9 449:23
varying 186:20
vascular 232:8
vascularization 72:3
vasculature 231:16 232:4
vasculitis 188:16
vast 154:16 188:18 218:8 354:18
VEGF 19:25 167:12,15 226:22 227:2,4 227:4,5,6,14 228:7,14,25 229:5,9,10,13 229:14 230:12

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 518 of 524

230:17,19
231:7,15,21
232:14,17,23
233:6,12,19
234:5,12,17
238:25 239:19
244:11,15
251:23 258:20
305:25 306:3
336:2,4,17
337:10 338:4
338:20 339:4,8
339:20,24
340:16,23,25
341:2 342:17
342:21 343:20
343:24 344:3,6
344:16,21,25
345:10,10,20
345:21 346:2
347:1,2,10,12
347:21 348:6
348:14 349:17
349:19 350:21
350:24 352:1
352:15 353:5
354:2,10
356:16,18
357:6,15 358:2
359:8,9 360:13
364:11,17
366:6 384:5
386:13 431:1
457:7
vein 36:18,19
37:13
verbatim 461:10
verification
442:2
verified 62:15
62:22 440:1
verify 52:24
53:8 61:10
245:4 246:9
291:23 317:23
version 435:20
436:8,10,18
439:18
versions 437:23
438:11
versus 9:13
12:17 115:25
118:3 158:22
255:10 283:15
415:6,6 416:20
vessels 231:23
231:24 232:21
viability 93:4,7
93:8,13,14,24
94:3,10,14
vial 174:16
176:18 177:2,4
177:7,8,15,16
178:5,9,12,22
179:2 180:12
189:23 253:9
257:9
vials 177:24,25
videographer
4:8 9:5,8 10:11
15:17 124:6,10
207:9 226:5,12
306:15,19
310:7 411:24
412:8 446:7,22
447:1 460:10
VIDEOTAPED
2:4
view 185:15
188:21,25
218:12 237:20
283:5,5 355:18
379:12,19
380:7,11 381:2
381:3,4,8,19
382:5,15 415:4
415:9,11,13
440:12
viewed 265:8
virtually 148:5
420:24
virtue 199:9
200:8 202:19
204:20 205:9
viscosities 222:1
295:1
viscosity 38:16
219:23,25
220:16,23
222:2,8,16
224:20 286:8
286:18,24
293:19 296:8
296:16,18
299:10 319:25
320:6 324:4
328:16,18
332:18 355:21
357:4 365:25
420:7,10,15
422:11,16,18
423:3,10,11,14
424:3,11 425:3
425:14 427:11
427:14,23
429:2 444:20
445:7 451:6
457:8,12
viscosity-lowe...
425:8,15,23
viscus 322:7
421:5,9
vision 144:20
182:8 274:1
379:21 405:7
visit 153:2
visits 262:2
visual 169:23
274:6 278:1
384:7 392:3
visualization
426:16
visually 177:9
vitamin 88:3
vito 88:3
vitrectomy 97:9
98:6
vitreoretinal
67:2,11 68:10
70:12 73:12
75:11,21 76:2
76:8,9,14 78:5
78:7,24 79:3
169:20 426:13
vitreous 97:10
97:12 98:23
99:10,19
100:10 103:3
103:14,16,21
104:1,4,21
109:10 112:22
114:5 191:20
451:3
Vitti 218:23
219:5,11,13,14
221:20 224:15
225:21 294:2
294:11 297:12
298:5 301:15
301:21,24
302:16,19
303:5,14,15
304:3,10,16,23
305:18,22,23
306:6 307:9,9
308:13,19
311:3,12,16
314:11 316:15
319:15 320:14
320:14,17,18
320:24 321:1,5
321:24 322:17
323:7,14,17
324:2,7,17
327:5,10,11,12
327:15,19
328:9 329:5,19
330:2,11,13,19
330:23,25
332:7,11 333:2
333:5,12,14,15
333:20 334:5
334:19,25
335:2,2,17,22
335:24 336:21
341:20 342:9
344:7,16
349:12,14
350:18 351:3
351:18,22
352:21,22
353:13 354:19
355:4 357:14
358:1,6,10,13
359:14,18
360:14,15,21
362:12,25
363:4,6 365:3
366:5 367:12
450:11 453:1,4
453:13,16,21
453:24 454:5,7
454:16 455:11
456:6 459:1,4
Vitti's 307:15
310:19 316:3,7
320:11 331:7
334:21 355:7
359:6,7 361:9
365:15,17
volume 38:23
100:17 101:5
101:11,14,17
101:18,19
102:11,19
103:2,10,14,16
103:21 104:1,4
104:21 105:12
105:14,18
116:17 189:15
189:17,21,23
190:21 191:2,2
191:15,20
192:3,8,14,21
193:1,6 195:17
220:15 240:6
287:2 294:22
295:23 296:4
297:20 298:2,2
298:4,15

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 519 of 524

299:22 300:7 300:12,14,20 301:10 302:15 307:20 309:5 309:18 312:11 313:6,11 314:10,10 318:18,19 319:1,7 321:16 322:23 328:12 332:16 335:10 354:20 357:9 361:24 363:1 364:8,12,15,19 366:10,16,17 367:15,16,19 370:17 371:1 401:10,25 402:5 409:19 421:3,7 424:12 425:3 429:3,24 430:17,19 431:9,13 432:8 443:19 444:5 444:20 445:4,5 451:3,4
volumes 190:2 294:24 302:7 302:11 312:5 328:23 431:3 431:24

W

wait 29:6 30:19 276:21
waiting 125:11 125:13 135:21 163:8 169:7 276:23 299:23
waive 462:10
walk 176:9,11 176:13 287:4
want 21:25 33:21 61:24 70:19 115:7,21 125:11 138:21 140:7 149:13 150:5 152:25 178:8,25 187:18 190:20 191:19 195:24 197:9 207:11 211:12,16 220:25 249:3 250:11 253:11 276:22 283:24 286:13 294:18 294:19,20,21 295:4,19 296:3 296:18,24 300:19,24 305:19 310:15 317:8,18 325:13 334:4 334:13 361:8 372:9 376:21 377:1 390:7 419:23 420:16 420:18,25 421:2 422:1 444:13 445:3 454:19,22 455:6
wanted 99:23,24 144:5 162:16 163:16,19,20 163:21,22,24 193:19 196:18 284:2 285:14 302:12 324:15 326:5 327:8 362:19 377:7 377:11 425:22 434:8
wants 366:15,16 445:5
wash 152:22
washing 100:3
Washington 1:24 3:20 463:3
wasn't 17:11 30:15 44:20 85:22,23 264:23 458:25 459:3
water 420:1,7,11 425:7,8,15,23
way 52:11 62:24 81:4 89:15 96:19 97:22 99:25 113:6 115:25 122:9 144:21 151:12 169:10,14 175:6 178:23 219:12 229:8 241:22 258:14 322:10 341:17 350:15 407:2 411:21 427:2
ways 97:21 112:17 261:12 283:11 393:18
we'll 14:5,5,6 46:1 161:10 286:11 450:2
we're 15:2 19:18 37:4 40:3 41:5 61:5 67:25 72:11 73:2 89:21 102:16 105:5 118:9 123:10 124:7 124:11 130:3 131:7 137:5 140:5 148:3 149:14 158:3 177:11 190:6 216:9 226:13 231:3 270:16 279:3 295:16 295:18 306:20 312:12 319:2 343:8,17 412:9 440:20 447:2 448:5 449:8 456:13 460:11
we've 67:19 89:1 95:2 104:18 135:14 146:10 182:19 259:24 260:3 275:24 282:14 291:9 294:13 327:6 377:16 419:1,4 435:4
weaknesses 154:14
wear 206:20
Web 155:22
week 26:9 44:3,6 44:14,21,25 45:7 71:6,8,9 71:11,12 133:22 134:2,4 162:21 168:9 273:14 278:2 280:19 281:5 439:7,9,10
weeks 99:10 133:17,17 152:13 162:7 248:15 273:9 275:6,12,15 277:16,22 279:1,6,8,8,17 279:18,19,22 280:1,3,4 281:14 379:20 379:22
weight 82:21 83:5 141:20 149:3 168:2,10 235:18 236:4 243:2,4 244:6 250:18
weights 83:2
Weill 68:23 70:15
welcome 124:13 194:12 196:11
well-documen... 267:13
well-known 367:23
well-respected 16:12
went 13:2,3 45:4 45:9,19 46:12 64:4 363:22 433:6 439:14
weren't 18:11 24:9 423:13 459:21
West 253:15 255:22
wet 41:15 151:22,25 249:22
When's 28:8 80:2 276:9
who've 143:9
wide 139:24 221:25 267:1 332:11 334:6,7
widely 130:17 171:2 188:21
widespread 136:17 239:14 261:6 386:12
Wild 253:15 255:22
willful 42:20
Williams 3:15 4:5 9:21,23,25 11:9
willing 168:8,10 318:2
wind 313:6
window 81:8
wish 145:24 154:17 155:23
withdraw 191:11 375:16 375:19
witness 8:3 10:10,13,21,24 23:8 26:22 28:22,24 45:18 46:5 95:10

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 520 of 524

124:4 125:8,15 173:20 207:16 207:20,23 226:3 249:9 270:7 276:20 277:2 289:25 290:22 314:2 372:10 411:23 418:14 456:20 456:24 460:9 462:2,9 463:8 463:23 464:4
witness's 28:20 36:9 444:7
woke 44:17
wonderful 133:20 362:16
Woo 107:2
word 33:6 45:25 74:3 88:6 101:2 111:9 112:22 113:9 122:10 127:23 162:25 172:17 178:13 189:8 268:15 291:4 335:21,23 338:12 340:11 341:6 343:24 360:24 375:19 387:19 389:7,9 389:11 394:23 414:14
wording 346:15
words 110:17 121:7 146:1 186:3 343:18 345:20 348:6 423:1
work 23:4 54:21 81:3 132:12 148:1 163:7 230:4 237:14 285:17 289:14 384:5
work-arounds 75:23
workable 363:16
worked 11:20 12:8 18:1,13 58:1 175:25 224:22 328:18 432:22,25
working 56:22 146:19 319:20 360:19 419:13
world 34:6,7 62:14 75:20 168:1
worse 14:6 266:21
worsened 186:7
worth 264:23
wouldn't 141:22 168:10 256:16 279:13 285:3 300:1 332:1 366:8 373:15 376:20,25 436:20
wound 421:15
wow 80:5 347:23
wrap 444:14
wrapped 121:6
write 213:2,5 215:21 288:16 288:19
writing 26:13 49:20 71:16
written 12:13 19:8 39:8 56:7 56:9,18,21,21 143:2 154:7,24 223:23 288:13 288:22 289:1,7 289:9 290:11 290:15,18 359:25 362:7 390:1 462:22
wrong 115:2 174:13 178:12 209:23 284:11 302:25 313:9
wrote 55:2,8 246:14,24

X

X 6:2 7:2 211:25
X-fold 84:11

Y

yeah 23:23,25 26:22 34:12 37:23 44:16 56:16 58:22 86:9 89:21 91:22 94:18 100:20 116:12 121:19 122:17 134:16,19 145:17 147:21 150:11 158:15 159:25 161:24 163:19 164:1 166:10 168:16 170:19 172:3 173:1,24 180:6 181:2 184:3,7 192:9 195:13 199:20 201:4 205:15 226:3 236:8 242:7 245:18,25 248:24,24 260:15 266:16 268:25 270:13 275:12 279:24 282:9 290:14 294:24 314:5 320:14 321:17 323:23 325:17 326:8 327:13 333:10 337:18 344:11 348:10 355:14 356:19 366:13 367:8 369:1,1 373:21 388:16 400:14 416:25 417:3 430:11 434:10 435:12 441:21
year 47:10 64:21 67:2 163:11,12 262:1 395:3
Year-and-a-half 18:18
years 18:18 19:13 65:22 68:16 70:8 80:4 147:3 157:6 197:21 198:3 202:25 246:15 392:13 393:1 397:20
Yep 270:4 383:2
yesterday 45:10 46:11
Yi 4:5 9:24
York 1:18,18 2:7 2:7 9:3,3,12,12 11:2 461:3
York-Presbyt... 68:23
young 69:25
younger 169:1

Z

zero 260:20
Zoom 4:4 23:17

0

0.05 312:19 429:25
0.075 306:2 330:14
0.1 131:24 132:3 137:14,15 139:7 140:15 140:16 298:19
0.15 299:5
0.2 298:19
0.25 299:5
0.3 188:4 240:10 241:5 243:8 248:14 249:25 261:2 298:19
0.35 299:5
0.4 298:19
0.45 299:6 312:20 313:6
0.5 188:4 225:15 264:10 266:22 271:13 273:6,7 274:14 277:12 277:14 298:19 326:14 379:22 393:4 394:3 414:7 415:13 454:11
0.55 299:6
0.6 298:20
0.7 298:20
0.70 298:7 324:3 444:18
0.75 336:15 339:3,22 345:8 346:24 353:3 354:8
0.8 298:20
0.9 225:6,10,13 298:20
00001 299:21
0001 299:9
036 31:18 32:2 32:10 33:4 34:21,23 36:25 37:19,23 38:2 39:9 199:6 212:1 220:4 222:23 237:9
06/02/26 462:3 463:9 464:3

1

1 48:25 100:25 100:25 126:23 127:12,24 131:24 133:3 137:14 140:14 149:9 198:21 205:11,22 207:20,22 218:21 219:3

Regeneron Ex. 2053
Alvotech v. Regeneron
PGR2025-00085
Page 521 of 524

222:22 225:24 269:13,13 270:10 271:1,9 272:17 275:3,4 275:14 283:5 284:18 305:9 390:5 394:2 450:6,9,10,21 451:22 464:5
1-inch 423:3
1-ish 207:19
1.0 436:11
1.25 252:23 253:3
1.5 103:2 349:15 350:20 354:1
1/2 100:25 103:19 253:6 313:24
1:35 226:13
10 211:25 212:2 222:5 278:21 308:22 310:23 337:2 340:24 349:15 350:20 351:13,15,16 353:25 361:11 391:10 449:13 449:22 454:11 457:14
10:55 124:7
100 38:10 190:11 219:16 224:16 303:20 305:24 306:2 307:20 308:7 308:19 309:3 310:20 313:16 313:19 314:10 314:18,21 316:2 319:7 320:20 321:15 321:16 322:4 322:23 330:15 330:24 331:10 336:1,16 337:8 337:9,10,20,21 338:3,15,20,23 339:1,3,19,23 341:1 343:3 346:25 349:16 349:19 350:9 350:20,23 351:15,25 354:1 361:11 362:13
1001 31:12,23 42:23
1003 40:10 447:21
1004 54:4,14 55:16 440:23
1007 304:24 453:17
1009 368:5 398:22 402:15
1010 419:8 454:23
102 246:10
1026 245:18 246:3,4 390:24 391:10 394:1 396:13
1034 272:8,15
1039 244:24 245:7 246:11 275:20 276:4 377:20,23,25 378:5 390:11
1048 7:7 247:9
1058 371:20,23 372:2,3,7,16 374:9 375:3,10 376:2
106 6:13
10th 68:2
11 5:7 212:3 450:5
11:17 124:11
110 209:24 298:5
114 235:23 237:10 384:17 384:25
114.3 39:3
115 219:15 220:21 225:1 293:18 297:12 297:15 301:16 301:19 302:14 304:4,11,19 319:18,24 320:4,9,15 321:24 327:21 328:10 331:18 331:22 332:5 332:14 334:11 334:22 335:10 335:11,13,16 337:23 338:5 338:23 352:24 354:17 355:6 355:17,18 356:1,15 361:25 363:2,6 363:15 365:17 367:12
116 210:2,7
118 210:22 211:21 212:19 212:24 216:10 448:6 452:12
1180 277:6
1182 378:5
1183 393:21
1199 140:2
12 49:19 102:2,3 207:17 272:11 273:8,14 279:22 380:23 385:8 392:5
12-week 282:12
12,168,036 1:11 31:9
12:57 226:6
1200 136:3,3
124 6:18
12860 3:6
129 273:22
12th 372:5
13 48:6,7 218:18
139 453:24 454:3
14 48:25 218:25 219:3
14-gauge 420:21
149 251:2
15 38:17 48:3,5 49:3 95:3 144:21 219:16 219:25 220:16 220:24 222:4 224:16,20 293:20 296:17 303:20 305:24 306:2 320:1 321:20 324:4 328:18 330:15 330:25 336:2 336:16 337:2 337:20 338:10 338:15 339:1,3 339:23 343:3,4 345:9 346:25 349:16 350:10 350:21 351:15 354:2 361:11 362:13 451:6
150 251:3 353:4 354:9 355:8 357:14 361:15 362:4 363:17 364:10,17 366:6
159 270:22 273:5 277:11 284:20
16 49:7 51:7 52:2 273:15 279:8,17 280:4 280:19
16-gauge 420:21
160 305:11
166 393:12 397:14
169 412:13 413:6
16th 50:3 52:21 53:3,4 60:7,16 60:19 61:19
17 49:11
172.5 355:20 356:17 358:1
1730 1:23 463:2
17th 18:23 25:1 41:25
18 42:23 179:1 194:17
180 456:18
183 40:23 456:15,19
184 40:15,24 41:3,11 456:23
196 308:2 311:24 315:4 320:13,18 321:19 322:9 322:10 323:14 331:11
197 307:8 308:1 308:23 311:24 319:4 321:4 322:9 323:9 329:12 331:23 333:23 359:14
1972 63:25
1977 65:3
198 311:25
1985 6:7,11 79:13 95:24
1992 6:16 106:20

2

2 1:20 49:3 198:1 199:1,2 212:7 253:6 265:6 269:13 270:14,15 271:5 272:21 273:6,7 274:13

275:18 276:19 277:6,13,14 278:9 280:18 281:4,13,20 283:5 284:20 293:20 326:14 326:15,15,18 370:6,11,15 379:20,25 390:6,9,16 392:13 394:3 394:20 395:15 396:18 397:20 397:20 400:19 401:6,23 404:16 409:16 412:22 414:8 415:13 416:22 464:6
2-inch 423:4
2.0 393:1 436:11
2:59 306:16
20 69:8 144:3 222:5 325:12 325:14 326:4,6 326:18 337:3 372:17,23 374:9,16 375:3 375:10 403:12 403:19 457:13
20-gauge 444:22
200 401:24
20024 3:20
20036 1:24 463:3
2006 68:20
2010 6:19 124:25
2012 246:11,15 372:5
2014 391:18,25
2018 68:3 144:4 144:18 145:1 145:18 148:15 157:13 163:17 163:25 168:22 171:8 191:24 193:12,21 199:8 218:11 224:9 236:14 236:17 237:4 239:8 247:25 248:10 249:16 252:6 263:4
202 1:24 463:4
202)-232-0646 462:16
202.434.5000 3:21
2025 18:23 25:1 42:1 50:3 51:7 52:2,21 53:3,4 60:16,19 61:19
2026 1:20 9:10 461:25 462:20
2041 6:6 79:11 79:16 80:7
2042 6:10 95:21 95:22
2043 6:14 106:17,18,25
2044 6:19 124:22,23
2045 7:6 247:6,7
205 349:5,11 352:6,13,20 353:9,21
206 334:15
21 270:23 284:19 372:17 374:9 375:3,10
22.5 353:4 354:9 355:9 357:15
226 5:10
23 231:11
232-0646 1:24 463:4
24 26:4 392:5
24-month 391:18
247 7:5
25 68:16 231:13 233:5 278:20 337:3 370:25 457:15
27 269:20
273 82:11
28 248:9 269:20 270:23
29 370:14,19
292 429:18,21 430:10
2nd 9:10

3

3 5:4 49:16 132:3 133:3 134:11,12 137:13,20 139:6 140:16 141:14,17 219:22 261:3 447:24 464:7
3:18 306:20
30 44:18 292:17 292:22 310:10 337:3 422:6
30-gauge 190:23 295:22 296:9 322:8 366:1 422:7,12 423:22 444:22
30-minute 445:21
31-gauge 322:8 356:24 422:6
32 113:18
34 114:8
35 337:4,5 399:2 399:4 402:15
36 113:21 114:16
38 222:23
391 42:9

4

4 5:4 49:7 101:1 103:19,19 214:13 222:23 266:24 269:19 271:11,12,15 273:7 274:12 274:21,23 277:14 278:9 281:21 312:14 313:24,24 314:12 326:15 395:6,11,14 399:20 400:18 400:23 401:5 401:21 402:7 404:8
40 69:8 236:25 337:6 360:3,9 360:20 402:2
400 3:7
41 227:8 228:13 234:1 235:15 235:16
412 5:11
42 235:15,16
43 371:8 373:4,5 374:22 379:1 387:7,22 389:6 389:16
43-gauge 420:23
44 269:25 270:6 271:10,17
447 5:8
45 272:21,24 390:3,4,10
458 5:9
48 113:21 114:16

5

5 38:16 49:11 83:9,10 219:25 220:16,24 222:4 224:20 296:17 306:1 313:24 314:12 320:1 324:4 328:18 330:14 330:24 336:15 337:2 339:2,22 340:22 343:3 345:8 346:24 351:4,12,14,16 353:3 354:8 361:15 362:4 392:17 451:6 461:25
5.0 335:25 436:11
5:00 411:25
5:29 412:9
50 190:10,12,15 190:17 191:17 225:6 253:3 294:22 295:18 299:15 300:12 300:17 309:11 309:18 312:11 312:17 314:9 316:13,16,20 318:17,24 319:10 322:5 337:6 363:24 365:21 370:17 371:4 430:1,18 431:3,9
52 273:15 279:18,19 280:19
59 109:4 412:14

6

6 5:5 276:17
6:00 446:23
6:15 447:2
6:26 460:11,14
60 69:11,13 113:7 190:16 299:15 322:5 337:6
65 238:9 242:22
66 209:18,21 240:8 242:22
67 209:23 243:12 245:22
68 250:11 448:5
680 3:19

69 412:14

7

7 1:17 2:6 5:5 9:12 297:17 359:13,25
7.5 336:1
70 38:23 220:15 225:3,5,19,22 297:20 298:10 299:1,15,16 301:9 322:1 328:13 332:16 337:7 354:21 362:23 363:1,5 363:10,20,25 364:8 365:12 365:19 367:15 368:2 443:20 444:5,21 451:4
70.09 297:16
7019 298:23
72 113:22 114:17 431:19
78 32:4
79 6:5 32:5

8

8 36:5 38:4 219:19 220:14 220:20 224:12 225:1 285:14 285:17,23 286:9,12 294:6 294:19 296:23 297:1,5,9,10 297:14,17 298:6,22 300:24 301:7,8 302:12 308:21 310:22 311:3,8 311:20 312:12 318:21 319:25 320:5 321:6,23 322:18 323:8 323:12,19 324:12,15 325:14,22,24 327:8,20,23 328:4 329:6,20 330:3,12,21,22 330:23 331:1 332:1,9 333:1 333:6,12,24 335:9 354:16 362:10,22,25 363:8 364:7 365:8,14 367:11 368:3 368:16,22 369:5,10 371:13 372:20 373:10,16 374:5,13 375:2 399:15,25 400:6,9 401:4 402:10,20 403:9,24 404:5 404:9,13,17 405:17,23,25 406:20 407:20 407:25 408:8 408:25 409:6 444:24 451:2
80 308:5,9,17 309:2,17 310:19 312:7,9 313:5,15,18 314:16,17 315:6,8,15 316:19 317:24 320:11,19 321:13 322:4 331:8 337:7
800 265:11 395:10
812 1:23 463:2
84 455:10
85 316:1 337:23 338:5
858.678.5070 3:9
86 455:5,10,13 455:22 456:1
87 336:9 352:10 352:15,18,20 353:2 357:25 358:6 361:7
89 197:10

9

9 103:20,21 297:17 308:22 310:22 312:16 312:18,19 447:25 455:20
9:00 1:19 2:7
9:11 9:2,10
90 197:13 198:22 199:2 200:12 201:8 202:14 203:7 203:19 204:8 204:11 225:13 240:6 243:9 300:14 308:6 308:18 309:2 310:20 313:16 313:18 314:17 316:3 320:12 320:20 321:14 322:4 331:9 337:8 357:22 363:22 365:20
90-ish 197:10
91 199:6 200:7 204:18
92 341:18,18 358:16
92130 3:8
93 341:21 357:22 358:17 358:19
94 306:7 308:12 336:10,11 339:11,21 340:7,12 341:8 341:23 342:9 343:8,18 346:3 346:19,24 347:19 348:5 348:19 357:22 358:11,19 362:12 363:7
95 6:9 201:1 341:25 358:21
96 113:22 114:17 320:24
97 329:24