UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

ALVOTECH USA INC. and ALVOTECH HF,

Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,

Patent Owner.

_____

Case PGR2025-00085

U.S. Patent 12,168,036.

_____

VIDEOTAPED DEPOSITION OF NEIL M. BRESSLER

Washington, D.C.

September 10, 2026

Job No. 649114

Pages 1-326

Reported by: Bethany Woodward, RMR, CRR, CRC, CSR

ALVOTECH 1080
Alvotech v. Regeneron
PGR2025-00085

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U.S. Patent 12,168,036.

_____

DEPOSITION OF NEIL M. BRESSLER, taken on behalf of the Petitioner, at 680 Maine Avenue SW, Washington, D.C. 20024 commencing at 8:09 AM, Thursday, September 10, 2026, reported by Bethany L. Woodward, RMR, CRR, CRC, CSR, CCR, RVR-M-S, pursuant to notice.

APPEARANCES:

For the Petitioner: FISH & RICHARDSON
BY: MEGAN CHACON
KRISTI SAWERT
12860 El Camino Real
Suite 400
San Diego, California
92130
(858)678-5070

For the Respondent: WILLIAMS & CONNOLLY LLP
BY: KATHRYN S. KAYALI
CHORONG SONG
680 Maine Avenue SW
Washington, DC 20024
(202)434-5000

Also present: GILBERT VOY

Videographer: AUSTIN COSTELLO

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Washington, D.C., Thursday, September 10, 2026 08:10:01

8:09 AM

08:08:53

THE VIDEOGRAPHER: Here begins Media 08:09:00
Number 1 in the videotaped deposition of 08:09:01
Neil M. Bressler in the matter of Alvotech USA 08:09:03
Inc., et al. v. Regeneron Pharmaceuticals, Inc., 08:09:08
in the United States Patent and Trademark Office; 08:09:08
Case Number PGR2025-00085. 08:09:16
Today's date is September 10th, 2026. 08:09:24
The time on the video monitor is 8:09. 08:09:27
The videographer today is Austin 08:09:32
Costello representing Planet Depos headquartered 08:09:35
at 451 Hungerford Drive, Suite 400, Rockville, 08:09:38
Maryland 20850. This video deposition is taking 08:09:42
place at 680 Maine Avenue, Southwest, Washington, 08:09:45
D.C. 20024. 08:09:51
Would counsel please voice-identify 08:09:54
themselves and state whom they represent. 08:09:56
MS. CHACON: Megan Chacon from 08:09:58
Fish & Richardson on behalf of the Alvotech 08:10:01
petitioners. With me today is my colleague, also 08:10:01

from Fish, Kristi Sawert. 08:10:04

MS. KAYALI: I'm Kathryn Kayali on 08:10:06

behalf of Patent Owner, Regeneron and the witness. 08:10:09

With me -- of Williams & Connolly. Excuse me. 08:10:10

And with me today is Chorong Song, also of 08:10:13

Williams & Connolly, and Gilbert Voy of Regeneron. 08:10:17

THE VIDEOGRAPHER: The court reporter 08:10:21

today is Bethany Woodward representing Planet 08:10:22

Depos. The witness will now be sworn and then we 08:10:24

can proceed. 08:10:27

NEIL M. BRESSLER, 08:10:28

produced as a witness by and on behalf of the 08:10:28

Petitioner, and having been first duly sworn, was 08:10:28

examined and testified as follows: 08:10:28

08:10:28

EXAMINATION 08:10:28

BY MS. CHACON: 08:10:37

Q Good morning, Dr. Bressler. 08:10:37

A Good morning. 08:10:40

Q How are you doing today? 08:10:40

A I'm fine. 08:10:42

Q Great. Well, as I just introduced 08:10:42

myself, my name is Megan Chacon from Fish. I'm here on behalf of Alvotech, and I'm going to ask you a few questions today. Okay? 08:10:44 08:10:47 08:10:50

A Okay. 08:10:51

Q All right. So before we get started, just a few preliminary questions. Have you been deposed before? 08:10:52 08:10:54 08:10:56

A I have not been deposed before. 08:10:57

Q So this is your first time in any deposition proceeding? 08:10:59 08:11:00

A This is my first time in any deposition proceeding. 08:11:02 08:11:04

Q Well, we will go through a few ground rules in a moment, but do you understand that you are here on behalf of Regeneron related to a proceeding before the Patent Trials and Appeals Board at the U.S. Patent and Trademark Office? 08:11:05 08:11:09 08:11:12 08:11:16 08:11:19

A I'm here in support of the patent owner. 08:11:23

Q Okay. And you understand that this is a proceeding before a body called the PTAB, does that sound familiar to you? 08:11:25 08:11:26 08:11:30

A I'm not familiar with the term "PTAB." 08:11:32

Q Okay. All right. So you understand that you were just sworn under oath for your testimony today? 08:11:35 08:11:37 08:11:40

A I am. 08:11:41

Q And do you understand that that testimony or that oath that you took is just the same as if we were at a court in front of a judge or a jury? 08:11:42 08:11:43 08:11:45 08:11:49

A I do understand that. 08:11:50

Q And so you understand that it's important today that you testify truthfully, accurately, and fully? 08:11:51 08:11:52 08:11:55

A I do understand that as well. 08:11:57

Q And, of course, you'll do that; right? 08:11:59

A I will do that. 08:12:01

Q Your attorney may object from time to time to some of my questions, but do you understand that unless she instructs you not to answer on the basis of privilege, that you need to respond and answer to my questions? 08:12:03 08:12:05 08:12:08 08:12:10 08:12:12

A I do understand that as well. 08:12:14

Q Okay. And if during today's proceeding 08:12:15

if you have any questions for me, if anything that I ask you is unclear or you would like me to rephrase something, will you ask me to do so? 08:12:19 08:12:24 08:12:27

A I will ask you to do so. 08:12:30

Q All right. Otherwise, if you respond, it's fair to assume that you've understood the question; correct? 08:12:31 08:12:33 08:12:36

A If I respond, it's fair to assume I understand the question. 08:12:42 08:12:44

Q Now, is there any reason you cannot give accurate, truthful, and complete testimony today; medical or otherwise? 08:12:46 08:12:49 08:12:51

A There is no reason for medical or otherwise. 08:12:53 08:12:56

Q Okay. And if that changes during the course of today's deposition, will you let me know right away? 08:12:56 08:12:58 08:13:00

A I will let you know promptly. 08:13:01

Q Thank you. 08:13:03

Now, we will try to proceed efficiently. We'll try to take a break every hour or so depending upon how you're feeling, but if you need 08:13:04 08:13:08 08:13:12

a break any sooner than that -- bio break or otherwise, just let me know. Okay? 08:13:14 08:13:18

A Thank you. Okay. 08:13:19

Q Okay. Let's talk about what you did to prepare for your deposition today. Can you just briefly describe your preparation, please? 08:13:25 08:13:30 08:13:33

MS. KAYALI: And I'll just caution the witness not to reveal the substance of attorney-client communications, but you can answer without doing so. 08:13:36 08:13:37 08:13:39 08:13:41

THE WITNESS: And -- so can you just repeat the question? 08:13:50 08:13:52

BY MS. CHACON: 08:13:53

Q What did you do to prepare for your deposition today? 08:13:53 08:13:55

MS. KAYALI: And -- sorry. Just for the record, I have to make the same caution, which is please don't reveal the substance of attorney-client communications, but you can answer without doing so. 08:13:56 08:13:57 08:14:00 08:14:01 08:14:03

THE WITNESS: To prepare for the deposition today, I had several meetings with 08:14:05 08:14:05

counsel to understand the process and practice answering questions. 08:14:10 08:14:23

BY MS. CHACON: 08:14:24

Q How many meetings did you have with counsel in preparation for your deposition today? 08:14:24 08:14:26

A I believe it was three meetings. 08:14:42

Q Approximately how much time did you spend preparing in each of those meetings? 08:14:47 08:14:49

A In preparing for the meetings, I reviewed the materials of my declaration again. And that was a few hours before each meeting. 08:14:54 08:14:56 08:14:59

Q How long was each meeting? 08:15:03

A Each meeting ranged from a few hours to about eight hours. 08:15:10 08:15:15

Q So when you say "a few hours," three to four? Does that sound right? 08:15:18 08:15:21

A I would estimate it was about four hours. 08:15:23 08:15:25

Q Okay. How much time in total have you spent preparing for your deposition today? 08:15:26 08:15:31

A I would estimate I've spent approximately 40 hours preparing for the 08:15:38 08:15:39

deposition today. 08:15:43

Q So you mentioned that you met with 08:15:55

counsel. Is it the counsel that's in the room 08:15:56

today? 08:15:59

A It is with Ms. Kayali and Ms. Song, and 08:16:00

then other counsel members walked in or were on a 08:16:07

Zoom, but I don't recall the names or who those 08:16:12

people were. 08:16:14

These were the principal -- these -- 08:16:15

Ms. Kayali and Ms. Song were the principal people 08:16:18

that I interacted with. 08:16:22

Q Okay. Aside from counsel, did you meet 08:16:23

with any nonlawyers in preparation for your 08:16:25

deposition today? 08:16:28

A I don't recall meeting with any 08:16:38

nonlawyers in preparation for the deposition. 08:16:39

Q Okay. So the only people that you met 08:16:42

with were the attorneys at Williams & Connolly. 08:16:44

Is that accurate? 08:16:47

A That's not accurate because, as I 08:16:50

recall, there were attorneys from Regeneron that 08:16:52

were on a Zoom during the meetings. 08:16:59

Q I see. Okay. So your prep consisted of preparing with the attorneys from Williams & Connolly and also in-house counsel at Regeneron? 08:17:02 08:17:05 08:17:07 08:17:09

A I would not characterize it that way because I never heard any comments from the people from Regeneron. 08:17:10 08:17:12 08:17:14

MS. KAYALI: So, again -- and I'll just caution you not to reveal the substance of attorney-client communication, but I think -- I think you can answer without doing so. 08:17:15 08:17:17 08:17:19 08:17:22

BY MS. CHACON: 08:17:39

Q Do you have any additional response? 08:17:39

A I have no additional response. 08:17:41

Q All right. As far as preparing for your deposition, did you select particular documents or things that you wanted to go over in preparation for your deposition? 08:17:56 08:18:00 08:18:05 08:18:07

MS. KAYALI: Again, please don't reveal the substance of attorney-client communications in your answer, but you can answer without -- to the extent you're able without doing so. 08:18:11 08:18:12 08:18:14 08:18:19

THE WITNESS: In preparing for the deposition, I did not select particular documents. 08:18:25 08:18:26

BY MS. CHACON: 08:18:30

Q Okay. So is it fair to say that the documents that you reviewed were selected by counsel? 08:18:30 08:18:33 08:18:34

MS. KAYALI: You can answer that "yes" or "no" so that you don't reveal the substance of attorney-client communications. 08:18:38 08:18:40 08:18:42

THE WITNESS: Yes. 08:18:45

BY MS. CHACON: 08:18:46

Q Are there any documents that you would have liked to have reviewed in preparation for your deposition but either didn't have a chance to or wasn't available to you? 08:18:46 08:18:49 08:18:52 08:18:54

A And can you just repeat the question? 08:19:03

Q Are there any documents that you would have liked to have reviewed in preparation for your deposition but either didn't have a chance to or they were not available to you? 08:19:05 08:19:06 08:19:08 08:19:10

A There were no documents to that nature. 08:19:12

Q And just to be clear, in terms of your 08:19:21

preparation, so I -- we'll get to this in a moment, but I know, during the course of this proceeding, you've had interactions with Dr. Berner Trout; is that correct? 08:19:25 08:19:28 08:19:29 08:19:31

A Can you just repeat the way you stated the question? 08:19:35 08:19:37

Q Sure. I want to confirm that you've had interactions with Dr. Bernard Trout in this proceeding. 08:19:38 08:19:40 08:19:43

A I had interactions with Dr. Trout. 08:19:47

Q Okay. And just to be clear, in preparation for your deposition today, you did not meet or speak with Dr. Trout? 08:19:52 08:19:55 08:19:57

A That is correct. 08:20:00

Q All right. Dr. Bressler, have you ever served as an expert witness before? 08:20:07 08:20:11

A I have served as an expert witness before. 08:20:14 08:20:16

Q Can you describe the context in which you were serving as an expert witness previously without revealing confidential information, but just generally the type of proceeding or subject 08:20:17 08:20:19 08:20:21 08:20:23

matter? 08:20:26

MS. KAYALI: Again, consistent with 08:20:27
Ms. Chacon's question, I'll caution you not to 08:20:31
reveal any third parties' confidential 08:20:32
information, but you can answer without doing so. 08:20:34

THE WITNESS: I served as an expert 08:20:40
witness to give opinions on a few malpractice 08:20:42
cases. 08:20:48

I'm not a legal expert, but I have been 08:20:53
asked in the past by U.S. Attorney Generals to 08:20:58
give opinions on Medicare issues -- fraud issues 08:21:01
as an expert witness, I believe. 08:21:13

And I've served as an expert witness 08:21:17
before the U.S. House of Representatives to 08:21:23
provide feedback on how IHS funding was used to 08:21:25
support vision-related research. 08:21:34

BY MS. CHACON: 08:21:40

Q You mentioned acting as an expert in 08:21:40
malpractice cases, and just to be clear, I 08:21:45
understand that to mean that you were providing 08:21:47
expert opinion related to somebody else's alleged 08:21:49
malpractice. 08:21:52

Is that a correct understanding? 08:21:56

A That is a correct understanding. 08:21:57

Q Now, were those cases involving angiogenic eye disorders? 08:21:58 08:22:01

A They were not. 08:22:10

Q Were they involving any use of any anti-VEGF drug medications? 08:22:15 08:22:18

A They were not. 08:22:21

Q You mentioned being asked to do some expert consulting work relating to U.S. House of Representatives and Medicare. 08:22:35 08:22:37 08:22:40

Have you ever testified before Congress? 08:22:41

A Not before Congress. That was before a subcommittee of the House appropriations committee. 08:22:45 08:22:46 08:22:52

Q Have you worked with the Williams & Connolly law firm before prior to this proceeding? 08:23:00 08:23:01 08:23:04

A I have. 08:23:06

Q In what context? 08:23:08

A There was another patent question in which I provided my opinions to their questions. 08:23:20 08:23:25

Q When you say "another patent question," are you referring to another patent proceeding, like the one that we're in now, or something different? 08:23:40 08:23:43 08:23:46 08:23:49

A It was not a deposition; it was providing information and discussing my expertise as it applied to the matters of what that patent "dispute," if that's the correct word, was. 08:23:50 08:23:54 08:24:01 08:24:06

Q Are you aware of whether or not that proceeding was before the PTAB or before a federal district court? 08:24:14 08:24:16 08:24:23

A As I said before, I don't know what a PTAB is -- or I can't recall what it is as a legal term. 08:24:25 08:24:27 08:24:30

Q Okay. So earlier, when I asked you if you've served as an expert in any other matter, you had listed malpractice cases for Medicare, U.S. House of Representatives. 08:24:30 08:24:35 08:24:38 08:24:41

Should we add, then, this other proceeding that you've worked with the Williams & Connolly firm with? Were you acting as an expert in that case? 08:24:43 08:24:46 08:24:47 08:24:55

A I was acting as an expert in that case. 08:24:56
Q Okay. So the list that you provided me 08:24:59
earlier was complete; right? We need to add that 08:25:01
other case that you were working on with 08:25:03
Williams & Connolly? 08:25:05
A I would add that other case as providing 08:25:06
expert expertise. 08:25:08
Q All right. And the other case where you 08:25:09
were providing expert expertise, is that related 08:25:11
to angiogenic eye disorders? 08:25:13
A It is related -- it was related to 08:25:19
angiogenic eye disorders. 08:25:22
Q Is it related to EYLEA? 08:25:25
A It was related to EYLEA. 08:25:26
Q Now, today, during the course of the 08:25:29
deposition, I'm going to make reference to EYLEA, 08:25:32
aflibercept, EYLEA HD. 08:25:35
Just to make sure we're clear on our 08:25:37
terminology, when I refer to "EYLEA," I'm going to 08:25:39
be referring to the 2 mg dose. 08:25:41
Will you understand that? 08:25:44
A I may understand that. It can be 08:25:45

confusing. And so, if possible, I would ask you to add the dosage at the end of the word "EYLEA." 08:25:47 08:25:49

Q I will try to do that. I may from time to time call it "EYLEA, EYLEA 2 mg, EYLEA low dose." Hopefully we'll understand each other with those synonyms. 08:25:53 08:25:56 08:26:02 08:26:04

Is that fair? 08:26:07

MS. KAYALI: Objection. Vague. 08:26:08

You can answer. 08:26:09

THE WITNESS: That may be fair, but I could easily make a mistake and assume you're talking about EYLEA 8 mg versus EYLEA 2 mg. 08:26:10 08:26:11 08:26:13

BY MS. CHACON: 08:26:18

Q And that's fine. And as we said at the beginning, if you do have any questions about what I'm asking for, you'll be sure to ask me; right? 08:26:18 08:26:20 08:26:23

MS. KAYALI: Objection. Foundation. 08:26:27

You can answer. 08:26:27

THE WITNESS: I may not realize that, so I'm -- I'm cautioning you to please try, if possible, to remember to put 2 mg at the end of EYLEA or 8 mg at the end of EYLEA. 08:26:28 08:26:30 08:26:34 08:26:37

BY MS. CHACON: 08:26:40

Q Sure. I will do my best to do that. 08:26:40

A Thank you. 08:26:43

Q And then, similarly, we might make reference today to EYLEA HD, the 8-mg dose. I will also try my best to say 8 mg, but if I don't, when I say EYLEA HD, I mean the 8-mg dose. 08:26:43 08:26:46 08:26:50 08:26:55

A That would be easier for me because I will look at EYLEA HD as synonymous with EYLEA 8 mg. 08:26:59 08:27:00 08:27:03

Q All right. Now, just turning back to a moment -- to the other proceeding that you're working on relating to EYLEA 2 mg, is that an ongoing proceeding; do you know? 08:27:07 08:27:11 08:27:14 08:27:22

A It is not for my involvement. 08:27:24

Q Okay. And were you working on that proceeding at the same time that you were also working on this proceeding? 08:27:25 08:27:29 08:27:32

A I was not. 08:27:34

Q Okay. Sticking with this proceeding before the PTAB, when were you first contacted by the Williams & Connolly law firm about being an 08:27:35 08:27:53 08:27:59

expert in this proceeding? 08:28:02

MS. KAYALI: And, again, I'll caution you not to reveal the substance of any attorney-client communication, but you can answer with respect to the timing that Ms. Chacon asked about. 08:28:04 08:28:05 08:28:08 08:28:12 08:28:17

THE WITNESS: I was contacted around the end of April of 2026. 08:28:19 08:28:21

BY MS. CHACON: 08:28:22

Q Do you recall who specifically contacted you? 08:28:22 08:28:29

A I believe, but I'm not certain, that it was through an email -- 08:28:44 08:28:47

MS. KAYALI: So, again, I'll caution you -- the witness not to reveal substance of any attorney-client communications. 08:28:52 08:28:53 08:28:55

But you can answer with respect to the person -- the identity of the person Ms. Chacon asked about, to the extent you recall. 08:28:57 08:29:03 08:29:08

THE WITNESS: I believe it was another counselor at Williams & Connolly named Teagan. 08:29:10 08:29:10 08:29:15

BY MS. CHACON: 08:29:18

Q Okay. So you mentioned that you were 08:29:18

contacted sometime around April 2026. When did 08:29:29

you actually begin work on this matter? 08:29:35

A Starting in May of 2026. 08:29:41

Q Do you recall when specifically in May 08:30:02

of 2026? 08:30:04

A I do not recall when. 08:30:05

Q Okay. Now, you submitted a declaration 08:30:07

in support of your opinions in this case. 08:30:16

Do you recall that? 08:30:18

A I do recall that. 08:30:19

Q And that declaration was submitted in 08:30:20

June of 2026; is that right? 08:30:23

A That is correct. 08:30:27

Q And just for the record, I see, 08:30:30

Dr. Bressler, that you brought some materials with 08:30:36

you. 08:30:38

What materials have you brought with you 08:30:38

to the deposition today? 08:30:40

A I brought a single-sided copy of my 08:30:41

declaration. I brought an additional copy of the 08:30:43

Table of Contents from that declaration. 08:30:50

I brought an additional copy of 08:30:52

Appendix B, the materials relied upon with that 08:30:52

that declaration. 08:30:52

And, finally, I created an additional 08:31:04

copy of the materials relied upon but in an 08:31:08

alphabetical order by last name of the first 08:31:15

author of the exhibits. 08:31:18

MS. KAYALI: And, Counsel, if you'd like 08:31:21

a copy of the... 08:31:22

MS. CHACON: We would. Thank you. 08:31:24

MS. KAYALI: Yeah. I trust you have the 08:31:25

other materials. That is the alphabetized 08:31:27

version. 08:31:30

MS. CHACON: I assume I do, but I do 08:31:30

need to ask Dr. Bressler. 08:31:33

BY MS. CHACON: 08:31:36

Q For the materials that you brought 08:31:36

today, are there any notes, markings, or other 08:31:37

notations in them? 08:31:40

A There are no markings or other notations 08:31:42

in any of the materials I just listed for you. 08:31:45

Q Okay. Thank you. 08:31:49

All right. So turning back to when you started working in this matter, you mentioned May 2026, and I had asked you if you specifically recall when. Sometimes I find it easy to kind of earmark things by looking at holidays. 08:32:05 08:32:07 08:32:09 08:32:12 08:32:19

Do you recall whether or not you began work on this matter before or after Memorial Day? 08:32:21 08:32:22

A I recall it was before Memorial Day. 08:32:33

Q Okay. Do you recall whether it was before or after Mother's Day? 08:32:36 08:32:39

A I do not recall that specific. 08:32:43

Q Okay. Now, in the time that you began work in May of 2026 to the time that you submitted a declaration in June of 2026, how much time did you spend working on contributing your thoughts to your declaration? 08:32:45 08:32:58 08:33:02 08:33:07 08:33:14

A The total time of reviewing the materials, of having interactions with counsel, to reviewing and editing drafts of the declaration, to finalizing it, I would estimate were about 60 hours. 08:33:17 08:33:19 08:33:23 08:33:29 08:33:32

Q So 60 hours over the course of two months, roughly speaking? 08:33:50 08:33:53

A Roughly speaking. 08:33:56

Q All right, Dr. Bressler. I know you brought a copy with you, but for posterity, I'm going to mark and hand you a copy of your report. 08:34:15 08:34:17 08:34:20

MS. CHACON: It's already been introduced in the proceeding as Exhibit 2052, so we'll go ahead and mark it as such. 08:34:22 08:34:23 08:34:26

And, Counsel -- 08:34:35

MS. KAYALI: I will add it to my pile. Yes. Thank you. 08:34:36 08:34:37

(Petitioner's Exhibit 2052 was marked for identification, the original of which is attached hereto.) 08:34:56 08:34:56 08:34:56

THE STENOGRAPHER: One second. 08:34:58

THE WITNESS: Thank you. 08:35:00

BY MS. CHACON: 08:35:04

Q All right. So you've been handed a copy of your declaration you submitted in this case. Feel free to take a look at it. I just have a few confirmatory questions for you. Let me know when 08:35:04 08:35:06 08:35:09 08:35:13

you're ready. 08:35:16

A I'm ready. 08:35:17

Q All right. So, Dr. Bressler, if you 08:35:18

could please turn to page 128 of your declaration. 08:35:21

Are you there? 08:35:38

A Okay. I'm there. 08:35:39

Q All right. So on page 128 of your 08:35:40

declaration, there is a signature there. Is that 08:35:42

your signature, Doctor? 08:35:46

A That is my signature. 08:35:47

Q Now, that looks like an e-signature; is 08:35:48

that correct? 08:35:51

A That is correct. 08:35:51

Q Do you typically sign things by 08:35:52

e-signature? 08:35:53

A I do typically sign things by 08:35:54

e-signature. 08:35:56

Q Okay. Now, it also notes that you 08:35:57

executed this on June 19th, 2026; is that correct? 08:35:59

A That is correct. 08:36:03

Q That's the date by which this was 08:36:11

submitted in the proceeding; is that right? 08:36:13

A I'm not sure when it was submitted in the proceeding. I know that I signed off on this final version on June 19, 2026. 08:36:16 08:36:18 08:36:22

Q Okay. So you don't know whether June 19th was the day that it was due or the day before it was due, do you? 08:36:25 08:36:26 08:36:29

A I do not. 08:36:32

Q Okay. Now, where were you located when you signed your declaration? 08:36:33 08:36:39

A I cannot recall exactly. I believe I was in Connecticut with my grandchildren. 08:36:43 08:36:47

Q So you were visiting family, visiting your grandchildren when you were signing off on your declaration? 08:36:59 08:37:01 08:37:03

A I vaguely recall that I was reviewing the final copy while I was there visiting them. I'm not certain, but that's my best recollection of where I was when I was signing it. 08:37:04 08:37:06 08:37:09 08:37:15

Q And I know time with grandchildren is precious. Do you recall approximately how much time you spent reviewing or working on the final version of your report before signing off on it 08:37:18 08:37:21 08:37:23 08:37:26

while you were visiting them? 08:37:28

MS. KAYALI: Objection. Vague. 08:37:30

THE WITNESS: Could you just repeat the 08:37:36

question? 08:37:37

BY MS. CHACON: 08:37:38

Q Sure. I said, "And I know time with 08:37:38

grandchildren is precious. Do you recall 08:37:41

approximately how much time you spent reviewing or 08:37:43

working on the final version of your report before 08:37:45

signing off on it while you were visiting them?" 08:37:48

MS. KAYALI: Objection. Vague. 08:37:51

THE WITNESS: I don't recall how much 08:37:54

time the day I signed it I was spending. I do 08:37:55

know that I spent many hours prior to June 19. 08:38:00

And then, on June 19, I was reviewing 08:38:06

the final copy to be sure I agreed with everything 08:38:11

that was in the final copy. 08:38:17

BY MS. CHACON: 08:38:18

Q Do you recall when you arrived in 08:38:18

Connecticut that week to visit your grandchildren? 08:38:23

A I do not recall. It might have been 08:38:26

that day or the day before. 08:38:28

Q All right, Doctor. I'm going to now have you just turn one page to Appendix A in what I handed you. And that appears to be a copy of your CV noting the revision date of June 15th, 2026; is that correct? 08:38:42 08:38:44 08:38:51 08:38:54 08:38:57

A That is correct. 08:39:00

Q All right. Now, it's been a few months since you submitted this. Are there any revisions, additions, supplements to your CV since you submitted this version? 08:39:01 08:39:04 08:39:10 08:39:13

A There may be one or two additional references after reference 500 since I submitted it. 08:39:34 08:39:35 08:39:38

Q Do you recall if any of those references relate to aflibercept? 08:39:44 08:39:45

A I cannot recall. I don't think so, and the only reason I said there might be one or two others is because, when I was updating a brief biography for an upcoming meeting, I noted that there were now over 500, not 500 references. 08:40:02 08:40:04 08:40:06 08:40:09 08:40:13

Q Thank you. 08:40:21

MS. CHACON: And to the extent 08:40:22

Dr. Bressler has an updated copy of the CV, Counsel, we would request that. 08:40:23 08:40:26

MS. KAYALI: We will consider it. Thank you. 08:40:31 08:40:32

BY MS. CHACON: 08:40:32

Q All right, Dr. Bressler. We're going to fast forward ahead a little bit here and turn to -- it's Appendix B, so right after your CV. Let me know when you're there. 08:40:32 08:40:42 08:40:45 08:40:51

A Okay. I'm there. 08:41:04

Q So you provided Appendix B, which says "Materials Relied Upon"; is that correct? 08:41:05 08:41:08

A That is correct. 08:41:12

Q What do you understand this document to be conveying? 08:41:13 08:41:15

MS. KAYALI: Objection. Vague. 08:41:17

THE WITNESS: I'm not a legal expert to know what the phrase from a legal perspective might mean, "Materials Relied Upon." 08:41:25 08:41:27 08:41:32

These are the papers and exhibits that were shared with me to consider in putting my declaration together. 08:41:35 08:41:37 08:41:41

BY MS. CHACON: 08:41:51

Q Okay. Did you prepare Appendix B 08:41:51

yourself? 08:41:53

MS. KAYALI: Objection. Vague. 08:41:53

THE WITNESS: I did not prepare this 08:42:03

table. 08:42:04

BY MS. CHACON: 08:42:05

Q Did you do anything to verify that it's 08:42:05

accurate? 08:42:09

MS. KAYALI: Objection. Vague. 08:42:09

You can answer. 08:42:10

THE WITNESS: I looked at this table 08:42:15

compared with the exhibits that I had, and the 08:42:17

listing appeared to match the listing of the 08:42:24

exhibits that I had. 08:42:25

BY MS. CHACON: 08:42:26

Q Okay. And, just to be clear, when you 08:42:26

say "the exhibits that I had," are you referring 08:42:28

to any and all exhibits that you had in your 08:42:31

possession, or any and all exhibits that you cite 08:42:34

in your declaration? 08:42:39

MS. KAYALI: Objection. Foundation. 08:42:41

Vague. 08:42:44
You can answer. 08:42:44
THE WITNESS: The list of exhibits that 08:42:49
I had to review in putting my opinion together for 08:42:50
this declaration. 08:42:57
BY MS. CHACON: 08:42:58
Q The heading in Appendix B has a footnote 08:42:58
to it, Footnote 1. Footnote 1 says, "This list is 08:43:14
not intended to be inclusive of all materials I 08:43:20
considered in forming my opinions." 08:43:22
Do you see that? 08:43:24
A I do. 08:43:24
Q So what materials, apart from what's 08:43:26
listed here in Appendix B, did you consider in 08:43:29
forming your opinions? 08:43:34
A The experience I have over the past 08:43:39
40 years in interpreting clinical research. 08:43:41
Q So when you include the Footnote 1 here, 08:43:49
it's meant to reflect your experience. Am I 08:43:52
understanding that correctly? 08:43:59
A Yes, where my experience would 08:44:00
include, for example, writing papers or reading 08:44:03

papers. 08:44:06

Q Okay. But there's no other, for 08:44:07

example, specific papers or exhibits to this 08:44:09

proceeding that you considered that are not listed 08:44:13

in this Appendix B? 08:44:16

MS. KAYALI: Objection. Foundation. 08:44:20

Vague. 08:44:23

You can answer. 08:44:24

THE WITNESS: Not that I recall. 08:44:28

BY MS. CHACON: 08:44:29

Q For the materials that are listed in 08:44:29

Appendix B, did you read each of them cover to 08:44:33

cover? 08:44:38

A I did not read each of them cover to 08:44:40

cover. 08:44:42

Q How did you decide which materials or 08:44:47

which references that are listed here to read 08:44:49

cover to cover? 08:44:54

A For some of them, if they involved, for 08:44:57

example, a clinical trial, I might review many 08:45:02

pertinent areas in that in order to help form my 08:45:07

opinion. 08:45:11

In others, I might look at a version or draft of what was being written to consider in this declaration, and I would then go to that exhibit and read through whatever I thought was pertinent to understand that paragraph or that statement in a draft of the declaration. 08:45:13 08:45:22 08:45:26 08:45:29 08:45:38 08:45:40

Q In preparation for your deposition today, are there any materials that are listed here in your "Materials Considered" list that you reviewed to refresh your recollection? 08:45:48 08:45:49 08:45:52 08:45:55

MS. KAYALI: Objection. Vague. 08:45:58

THE WITNESS: Please repeat the question. 08:46:02 08:46:03

BY MS. CHACON: 08:46:03

Q In preparation for your deposition today, are there any materials that are listed here in Appendix B that you reviewed to refresh your recollection? 08:46:03 08:46:06 08:46:08 08:46:11

MS. KAYALI: Objection. Vague. 08:46:13

THE WITNESS: I do recall in preparation for the deposition, going back to some of the specific exhibits to remind myself of details that 08:46:17 08:46:21 08:46:25

were in the declaration. 08:46:29
BY MS. CHACON: 08:46:30
Q Which ones? 08:46:30
A That would be hard to guess on them. I could start going through the list and tell you if I recall looking at them or not, if you would like me to. 08:46:36 08:46:39 08:46:42 08:46:45
Q There's none that stand out in your mind? 08:46:46 08:46:48
MS. KAYALI: Objection. Asked and answered. 08:46:49 08:46:50
THE WITNESS: There -- none that stand out in my mind. There are many that I know I re-reviewed to remind myself what I considered in putting together the declaration. 08:46:52 08:46:54 08:46:57 08:47:03
BY MS. CHACON: 08:47:05
Q Can you give me a few examples? 08:47:05
MS. KAYALI: Objection. Vague. 08:47:07
You can answer. 08:47:10
THE WITNESS: I recall looking at the Vitti, Exhibit 1007. I recall looking at the declaration of Dr. D'Amico, Exhibit 1003. I 08:47:16 08:47:16 08:47:26

recall looking at Exhibit 1026, the Allen Ho 24-month efficacy and safety of 0.5 to 2 mg ranibizumab. 08:47:33 08:47:37 08:47:41

I recall looking at Exhibit 1039, the Michael Stewart clinical and differential utility of VEGF. 08:47:45 08:47:49 08:47:52

BY MS. CHACON: 08:47:56

Q Okay. Great. Thank you. 08:47:56

MS. KAYALI: Sorry, Dr. Bressler. Were you finished with your answer? 08:47:58 08:47:59

THE WITNESS: Those were examples. I could go on, if you want me to. 08:48:03 08:48:04

BY MS. CHACON: 08:48:05

Q That's okay, Dr. Bressler. 08:48:05

A Thank you. 08:48:08

Q So I want to turn now, Dr. Bressler, to talking a little bit about the scope of your work -- of your declaration. 08:48:23 08:48:26 08:48:29

And if you could please turn to page 72 of your declaration where you included a table as part of paragraph 143. Just let me know when you're ready. 08:48:32 08:48:35 08:48:40 08:48:44

Are you there, Doctor? 08:49:26

A I am. I'm just reviewing so I can 08:49:28
remind myself what this section was about. 08:49:30

Thank you. I'm there. 08:49:58

Q Okay. Great. Now, you -- do you 08:49:59
understand that this proceeding at the PTAB 08:50:01
relates to U.S. Patent 12,168,036? 08:50:04

A I do. 08:50:12

Q And, for purposes of the deposition, 08:50:13
I'll refer to it as "the '036 patent." If I do 08:50:15
so, will you understand what I mean? 08:50:19

A I will. 08:50:21

Q Okay. Now, is it your understanding 08:50:22
that Alvotech has alleged that the claims of the 08:50:24
'036 patent are invalid on various grounds? 08:50:29

MS. KAYALI: Objection. Vague. 08:50:44

You can answer. 08:50:44

THE WITNESS: As I said in the 08:50:45
declaration in paragraph 143, I understand that 08:50:46
the claim in the '036 patent were being stated as 08:50:52
to have been obvious in various combinations of 08:51:01
references by Alvotech. 08:51:03

BY MS. CHACON: 08:51:05
Q And -- 08:51:05
A And -- so I don't know if that's what 08:51:07
"invalid" means. 08:51:09
Q So do you have an understanding of what 08:51:17
it means for a patent to be invalid? 08:51:19
MS. KAYALI: Objection. Vague. Calls 08:51:21
for a legal conclusion. 08:51:24
You can answer. 08:51:26
THE WITNESS: It sounds like a 08:51:30
legal -- legal term that I cannot define for 08:51:30
you. 08:51:34
BY MS. CHACON: 08:51:35
Q And in preparing your opinions today, 08:51:35
did you consider or understand that there are 08:51:42
legal principles that are to be applied in terms 08:51:52
of your analysis? 08:51:55
MS. KAYALI: Objection. Vague. 08:51:58
You can answer. 08:51:59
THE WITNESS: I understand there are 08:52:03
legal standards that are used in helping to form 08:52:04
my opinion. 08:52:11

BY MS. CHACON: 08:52:12

Q Okay. And maybe I should use another 08:52:12

term as well just in case we're misunderstanding 08:52:14

each other. 08:52:16

Do you understand that Alvotech has 08:52:17

alleged that the claims of the '036 patent are 08:52:19

unpatentable? 08:52:23

MS. KAYALI: Objection. Vague. Calls 08:52:25

for a legal conclusion. 08:52:29

You can answer. 08:52:30

THE WITNESS: Again, I know that they 08:52:31

claim to have been obvious in view of various 08:52:32

combinations of references. 08:52:34

BY MS. CHACON: 08:52:35

Q Now, the table that you provide in 08:52:35

paragraph 143, does that recite the combinations 08:52:43

that you're addressing in your declaration? 08:52:49

A It does address combinations that I'm 08:52:58

addressing in my declaration. 08:53:00

Q Okay. And when I look at the table and 08:53:02

I look at the grounds, I see Ground 1, and I see 08:53:06

Ground 2. And it looks like Ground 2 is the same 08:53:12

as Ground 1. 08:53:17

Do you see that? 08:53:19

A I do see that. 08:53:23

Q So what Ground 2 are you addressing in your declaration? 08:53:24 08:53:27

A I'm not aware of what the grounds are that are listed there. 08:53:39 08:53:41

Q So you don't know what Ground 2 is? 08:53:43

MS. KAYALI: Objection. Foundation. 08:53:47

THE WITNESS: I'm not certain from a legal standard how that's being used. 08:53:51 08:53:52

BY MS. CHACON: 08:53:54

Q Do you know what references that you were attempting to address when addressing Ground 2 in your declaration? 08:53:54 08:53:57 08:54:01

MS. KAYALI: Objection. Vague. 08:54:06

THE WITNESS: In addressing my declaration, in considering these claims in the second column, I was considering the various references that are in the third column. 08:54:08 08:54:10 08:54:12 08:54:16

BY MS. CHACON: 08:54:19

Q So you were considering Vitti, the AU 08:54:19

EYLEA label and Larson twice? 08:54:27

MS. KAYALI: Objection. Foundation. 08:54:32

THE WITNESS: I was referring to those 08:54:37

for -- for Claims 1 and 4 through 38. 08:54:41

BY MS. CHACON: 08:54:48

Q And do you know if Ground 2 includes any 08:54:48

other prior art references aside from what you see 08:54:52

listed here in the table in paragraph 134 of your 08:54:55

declaration? 08:54:58

A Again, I'm not familiar with what the 08:54:59

legal term is for grounds. 08:55:01

Q Well, you see you have a table here, 08:55:04

Dr. Bressler, and it includes the word "ground." 08:55:07

Do you know what "ground" here means in 08:55:10

reference to the table you provided in your 08:55:13

declaration? 08:55:15

MS. KAYALI: Objection. Vague. 08:55:15

You can answer. 08:55:18

THE WITNESS: I only looked at this 08:55:22

table in terms of the claims and Alvotech's 08:55:23

combination of references that were being used for 08:55:26

those claims. 08:55:29

BY MS. CHACON: 08:55:30

Q So, again, do you know what the word 08:55:30

"ground" means in the table that you provided? 08:55:38

MS. KAYALI: Objection. Asked and 08:55:41

answered. 08:55:43

THE WITNESS: I do not know what the 08:55:44

term "ground" means from a legal perspective. 08:55:45

BY MS. CHACON: 08:55:48

Q So sitting here today, Doctor, do you 08:55:48

know whether or not the inclusion of the same 08:55:58

combination of references for Ground 2, as was 08:56:04

provided in Ground 1, was a mistake? 08:56:07

MS. KAYALI: Objection. Foundation. 08:56:12

You can answer. 08:56:12

THE WITNESS: I do not think it was a 08:56:17

mistake. 08:56:18

BY MS. CHACON: 08:56:19

Q Okay. Prior to submitting your 08:56:19

declaration on June 19th, which we established was 08:56:31

the final version here, did you review the 08:56:38

entirety of your declaration? 08:56:42

A I did review the entirety of the 08:56:44

declaration. 08:56:46

Q How carefully would you say you reviewed it? 08:56:47 08:56:49

MS. KAYALI: Objection. Vague. 08:56:49

You can answer. 08:56:50

THE WITNESS: There were portions that I reviewed extremely carefully, and those usually dealt with areas from my expertise from a clinical -- from a clinician. 08:56:53 08:56:54 08:57:01 08:57:05

BY MS. CHACON: 08:57:06

Q Did you review your declaration cover to cover before you signed off on it? 08:57:06 08:57:08

A I did review my declaration cover to cover before I signed off on it. 08:57:10 08:57:12

Q How much time did you spend reviewing your declaration before signing off? 08:57:14 08:57:16

A I spent many hours reviewing multiple drafts of my declaration before I signed off. 08:57:21 08:57:25

Q I'm just talking about the final version, Dr. Bressler. How much time did you spend reviewing the final version before you signed off? 08:57:29 08:57:30 08:57:32 08:57:35

MS. KAYALI: Objection. Vague. Asked and answered. 08:57:36 08:57:38

THE WITNESS: I spent many hours reviewing the final draft in the last day or two or three before June 19, and then would spend a little time if there was a Track Change towards the end of those final versions, believing that I was given a copy of what I had already reviewed very carefully before and that the Track Changes were the only changes subsequent to something given previously to me. 08:57:43 08:57:45 08:57:51 08:58:00 08:58:07 08:58:12 08:58:15 08:58:19 08:58:21

BY MS. CHACON: 08:58:23

Q So when you say how many -- you say "many hours" in the few days leading up to the final version, how many hours, approximately? 08:58:23 08:58:27 08:58:30

MS. KAYALI: Objection. Vague. 08:58:34

THE WITNESS: I would estimate maybe 10 hours, maybe more. 08:58:41 08:58:41

BY MS. CHACON: 08:58:43

Q And so leading up to your signature of your declaration, you mentioned that you might spend a little bit of time reviewing some Track 08:58:43 08:59:01 08:59:03

Changes. 08:59:06

Did I understand you correctly? 08:59:07

MS. KAYALI: Objection. Foundation. 08:59:09

THE WITNESS: Before signing off on the final version, there may have been one or two additional Track Changes that I confirmed were as discussed. And once confirming that, I signed the final version. 08:59:15 08:59:16 08:59:19 08:59:27 08:59:32

BY MS. CHACON: 08:59:33

Q Now, did you review the entirety of your declaration in preparation for your deposition today? 08:59:33 08:59:42 08:59:45

A I did. 08:59:46

Q In reviewing your declaration, did you identify any mistakes that you would like to correct? 08:59:48 08:59:51 08:59:55

A There was one mistake, as I recall. I can't find it now. I was looking at something on page 63 in paragraph 124, and it may not be exactly that section, where in the last sentence, it says "about 23 days sooner." 09:00:01 09:01:55 09:01:57 09:02:04 09:02:11

And I thought, when I was reviewing 09:02:12

this, the math was off by one day, and that's the only one that I can recall. 09:02:14 09:02:18

Q Okay. So just to orient ourselves, paragraph 124 relates to your opinions as to the CLEAR-IT 2 trial? 09:02:24 09:02:26 09:02:31

A That is correct. 09:02:36

Q Okay. And you believe that there -- in paragraph 124, that there was an error here in terms of the number of days that you reported? 09:02:36 09:02:38 09:02:45

A It might have been there or in another section on the number of days comparing the treatment regimens. 09:02:48 09:02:50 09:02:52

Q Okay. Well, during the course of the deposition today, Dr. Bressler, if you recall specifically where that error is, will you let me know? 09:02:54 09:02:57 09:03:00 09:03:02

A Absolutely. 09:03:03

Q Thank you. 09:03:03

Dr. Bressler, does your declaration include all of the opinions that you intend to offer in this proceeding? 09:03:12 09:03:15 09:03:16

MS. KAYALI: Objection. Vague. 09:03:18

THE WITNESS: The declaration is my opinion on the assignment that I was given. 09:03:26 09:03:27

BY MS. CHACON: 09:03:31

Q And it includes all the opinions that you intend to offer in this case? 09:03:31 09:03:34

A Again, I'm concerned that there may be a legal definition, but to the best of my understanding of your question, these are the -- all the opinions that I plan to share with you in the case -- or in the matter. 09:03:45 09:03:48 09:03:51 09:03:53 09:03:56

Q So I know you brought with you a copy of your Table of Contents, and there's also a Table of Contents in the exhibit that I handed you, so feel free to refer to either, whatever you prefer. 09:04:09 09:04:11 09:04:13 09:04:16

A Thank you. 09:04:18

Q But I do want to take a look at that Table of Contents, so if you can pull that up, please. 09:04:19 09:04:21 09:04:24

A Okay. I'm there. 09:04:25

Q Now, I want to understand sort of the major segments of your declaration here. So you do provide, in Section 7, a summary of the State 09:04:32 09:04:35 09:04:40

of the Art as of May 2018; is that correct? 09:04:45

A That is correct. 09:04:49

Q And then you also provide some 09:04:50

background information on EYLEA HD; correct? 09:04:52

MS. KAYALI: Objection. Vague. 09:04:59

You can answer. 09:05:00

BY MS. CHACON: 09:05:01

Q In Section 8, in case you're wondering. 09:05:01

A Section 8 is about EYLEA HD. 09:05:04

Q And then in Section 9, you have a 09:05:07

section entitled "The POSA would not have been 09:05:09

motivated to administer an 8-mg dose aflibercept 09:05:13

to treat angiogenic eye disorders with a 09:05:16

reasonable expectation of success." 09:05:18

Do you see that? 09:05:21

A I do see that. 09:05:21

Q What did you intend for this section to 09:05:23

cover? 09:05:25

MS. KAYALI: Objection. Vague. 09:05:27

THE WITNESS: I intended this section to 09:05:30

cover why a POSA would not have been motivated to 09:05:32

administer an 8-mg dose to treat angiogenic eye 09:05:39

disorders with a reasonable expectation of success. 09:05:40 09:05:42

BY MS. CHACON: 09:05:43

Q All right. And you include three, sort of, subsections or subcategories within that; correct? 09:05:43 09:05:49 09:05:52

A That is correct. 09:05:54

Q All right. And in the remainder of your sections appear to provide opinions on things that a POSA, or a Person of Ordinary Skill of the Art, would have either desired or would not have understood. 09:05:55 09:06:01 09:06:04 09:06:09 09:06:13

Is that a fair characterization of Sections 10, 11, 12, and 13? 09:06:14 09:06:16

MS. KAYALI: Objection. Foundation. Vague. 09:06:19 09:06:20

THE WITNESS: Would you just repeat the question? Thank you. 09:06:29 09:06:31

BY MS. CHACON: 09:06:32

Q The remainder of your sections appear to provide opinions on things that a POSA, or Person of Ordinary Skill of the Art, would have either 09:06:32 09:06:35 09:06:40

desired or would not have understood. 09:06:42
And I asked if that was a fair 09:06:45
characterization of the sections? 09:06:48
MS. KAYALI: Objection. Vague. 09:06:50
THE WITNESS: Characterizing my opinion 09:06:52
is really based on the entire declaration. These 09:06:52
sections contain exactly what's written in the 09:06:55
titles here in the Table of Contents. 09:06:59
BY MS. CHACON: 09:07:02
Q Okay. At least the first two, 09:07:02
Sections 10 and 11, relate to things that a POSA 09:07:04
would have desired; right, those two sections? 09:07:09
A That is correct. 09:07:12
Q And the other two sections, 12 and 13, 09:07:12
are things that a POSA would not have understood; 09:07:16
correct? 09:07:19
MS. KAYALI: Objection. Vague. 09:07:20
THE WITNESS: That is correct. I can 09:07:21
read the entire section titles for you, because 09:07:22
it's -- 09:07:27
MS. CHACON: No, that's fine. 09:07:28
THE WITNESS: -- specific -- 09:07:29

MS. KAYALI: Please allow the doctor to finish his answer. I don't believe he was finished. 09:07:30 09:07:31 09:07:33

THE WITNESS: Because it has more than the phrase that you said. 09:07:33 09:07:37

BY MS. CHACON: 09:07:38

Q Sure. And I don't think that's necessary for right now. 09:07:38 09:07:40

MS. KAYALI: Again, I'll ask you to please allow the witness to finish his answers before speaking over him. 09:07:43 09:07:44 09:07:46

MS. CHACON: Are you ready, Doctor? 09:07:50

THE WITNESS: I'm ready. Thank you. 09:07:52

BY MS. CHACON: 09:07:53

Q All right. Now, earlier we had looked at a table with the grounds. And in that table, it had also identified claims of the '036 patent. 09:07:53 09:07:59 09:08:01

Do you recall that? 09:08:06

A I do recall that. 09:08:07

Q Okay. I'm looking here at your Table of Contents, and you don't have any sections in your declaration that go through analysis of each of 09:08:08 09:08:09 09:08:15

the challenged claims of the '036 patent, do you? 09:08:21
MS. KAYALI: Objection. Foundation. 09:08:26
Vague. 09:08:31
You can answer. 09:08:31
THE WITNESS: Starting on page 18, 09:08:49
paragraph 38, I have a list of the challenged 09:08:50
claims. 09:08:53
BY MS. CHACON: 09:08:54
Q I see that. Now, is there anywhere in 09:08:54
your declaration where you go through, for 09:09:00
example, a specific analysis of why Claim 31 is 09:09:03
not unpatentable? 09:09:11
MS. KAYALI: Objection. Vague. Lacks 09:09:14
foundation. 09:09:16
THE WITNESS: There are sections 09:09:33
throughout my declaration where I refer to some of 09:09:34
the claims. 09:09:39
BY MS. CHACON: 09:09:40
Q Okay. But to be clear, Dr. Bressler, 09:09:40
you don't have a section for each individual 09:09:44
claim; is that correct? 09:09:47
MS. KAYALI: Objection. Foundation. 09:09:48

Vague. Asked and answered. 09:09:51

THE WITNESS: I don't have a section in 09:09:55

the Table of Contents that lists each -- each 09:09:57

claim. 09:10:01

BY MS. CHACON: 09:10:02

Q So, to be clear, do you -- so you don't 09:10:02

address unpatentability on a claim-by-claim basis; 09:10:20

correct? 09:10:24

MS. KAYALI: Objection. Calls for a 09:10:25

legal conclusion. Asked and answered. And lacks 09:10:25

foundation. 09:10:27

THE WITNESS: If you ask me about a 09:10:31

specific section and it refers to a specific 09:10:32

claim, I am more than happy to review that with 09:10:35

you. 09:10:37

BY MS. CHACON: 09:10:37

Q Sure. And I would be happy to, 09:10:37

Dr. Bressler, but that's why I took you to your 09:10:40

Table of Contents, because I don't see a 09:10:43

particular section that addresses each individual 09:10:45

claim. 09:10:48

So I just want to understand the scope 09:10:48

of what claims, what you're addressing in your declaration. 09:10:50 09:10:53

So, to be clear, is there anywhere in your declaration where you walk through your analysis for each claim that Alvotech has alleged is unpatentable? 09:10:54 09:10:58 09:11:02 09:11:06

MS. KAYALI: Objection. Lacks foundation. Asked and answered. 09:11:08 09:11:09

THE WITNESS: The declaration addresses my opinion on the challenged claims. 09:11:19 09:11:20

BY MS. CHACON: 09:11:22

Q Dr. Bressler, you are a clinician; correct? 09:11:22 09:11:52

A That is correct. 09:11:53

Q And you said you've been researching, practicing for 40-plus years. Did I hear that correctly? 09:11:55 09:11:59 09:12:01

A That is correct. 09:12:02

Q Okay. You're not a formulating expert, are you? 09:12:02 09:12:08

A I am not a formulating expert. 09:12:09

Q Have you ever worked on the formulation 09:12:13

of a drug? 09:12:15

A I have never worked on the formulation 09:12:17

of a drug. 09:12:19

Q And, Dr. Bressler, you're not a 09:12:22

statistician; correct? 09:12:26

A I am not a statistician; correct. 09:12:29

Q Have you ever worked on any formulation 09:12:38

related to aflibercept? 09:12:40

A I've never worked on any formulation 09:12:43

related to aflibercept. 09:12:46

Q Never worked on any formulation related 09:12:48

to any other large molecules or proteins? 09:12:51

A I have never worked on any other 09:12:55

formulations of what you just said including large 09:12:55

proteins. 09:12:57

Q Have you ever measured the viscosity of 09:12:59

a drug product before? 09:13:02

MS. KAYALI: Objection. Vague. 09:13:04

You can answer. 09:13:05

THE WITNESS: I have not done so in the 09:13:10

last 40 years. I cannot tell you whether during 09:13:11

college in chemistry or physics I worked on 09:13:14

viscosity. 09:13:20
BY MS. CHACON: 09:13:20
Q So at least in the last 40 years you 09:13:20
haven't measured the viscosity of a drug product; 09:13:24
correct? 09:13:27
A Correct. In the last 40 years, I have 09:13:28
not worked on the viscosity of a drug product. 09:13:30
MS. KAYALI: And, Dr. Bressler, I would 09:13:33
just ask if you can give me a beat to object. I 09:13:35
was intending to object to that question as vague, 09:13:40
but we can move on. 09:13:42
BY MS. CHACON: 09:13:43
Q Now, as part of your role as a 09:13:43
clinician, do you do any research or study of the 09:13:46
viscosity of drug products? 09:13:48
A As part of my role as a researcher, I do 09:13:54
no studies on viscosities of a product. 09:13:59
Q Dr. Bressler, I know in your declaration 09:14:24
you make reference to a couple of communications 09:14:27
that you had with Dr. Trout; is that correct? 09:14:31
A That is correct. 09:14:37
Q Who is Dr. Trout? 09:14:39

A Dr. Trout, I understand, is an expert in formulation of drugs. 09:14:50 09:14:56

Q Did you know Dr. Trout prior to working on this matter? 09:15:03 09:15:04

A I did not know him prior to working on this matter. 09:15:05 09:15:08

Q When did you first meet Dr. Trout? 09:15:10

A I first met him on June 10, 2026, as written in the declaration on page 4. 09:15:14 09:15:19

Q And, prior to your first meeting with him on June 10th, 2026, did you have any written communications with Dr. Trout? 09:15:26 09:15:29 09:15:32

A I did not have any written communications with Dr. Trout prior to June 10, 2026. 09:15:34 09:15:36 09:15:39

Q Okay. So I see that there is on page 4, a meeting, so we're going to start with the first one on June 10th, 2026. 09:15:41 09:15:43 09:15:46

Can you describe to me what precipitated the meeting with Dr. Trout on June 10, 2026? 09:15:49 09:15:54

MS. KAYALI: You can answer that. 09:15:58

But I'll caution the witness not to 09:15:59

reveal the substance of any attorney-client communications. 09:16:02 09:16:04

To the extent you can answer without doing so, please feel free. 09:16:04 09:16:06

THE WITNESS: I was asked by counsel to -- 09:16:09 09:16:10

MS. KAYALI: And, again, I'll caution you not to reveal the substance of attorney-client communications, but you can answer to the extent you are able to do so. 09:16:10 09:16:12 09:16:15 09:16:18

THE WITNESS: I was asked by counsel to provide my expertise as a clinician to Dr. Trout. 09:16:21 09:16:22

BY MS. CHACON: 09:16:27

Q Do you know whether Dr. Trout requested to understand your expertise? 09:16:27 09:16:37

A I -- I do not know if he requested my expertise. 09:16:40 09:16:43

Q Okay. So the meeting that took place on June 10th, 2026, was that in-person? Remotely? How did it take place? 09:16:44 09:16:47 09:16:54

A It was remotely by Zoom. 09:16:55

Q How long did the June 10th meeting last 09:17:00

for? 09:17:03

A It was approximately 30 minutes. 09:17:06

Q Was there anyone else on the call that participated in that meeting besides you and Dr. Trout? 09:17:14 09:17:17 09:17:19

A I recall Ms. Kayali was in the Zoom meeting. I vaguely recall there may have been one or two other people from Williams & Connolly on the call, but I cannot be certain of that. I am certain that Ms. Kayali was on the call -- was on the Zoom. 09:17:20 09:17:25 09:17:28 09:17:31 09:17:34 09:17:41

Q Was there anyone from Regeneron on the call? 09:17:42 09:17:46

A That, I cannot recall. 09:17:47

Q Can you describe for me, sort of how the call on June 10th went? 09:17:50 09:17:52

MS. KAYALI: Objection. Vague. 09:17:54

THE WITNESS: I recall explaining how I use anti-VEGF to treat retinal diseases as I might explain to a patient in very general terms. 09:17:56 09:18:03 09:18:12

BY MS. CHACON: 09:18:18

Q So you joined the call. Did you start 09:18:18

off with pleasantries or background, that sort of thing? 09:18:24 09:18:28

MS. KAYALI: Objection. Vague. 09:18:29

THE WITNESS: I can't recall except to perhaps say, "Hello, nice to meet you" pleasantry. 09:18:31 09:18:37

BY MS. CHACON: 09:18:42

Q Okay. Were there any particular questions that Dr. Trout was interested in that you came prepared to address? 09:18:42 09:18:45 09:18:47

MS. KAYALI: Objection. Compound. 09:18:54

THE WITNESS: I didn't come prepared to answer anything other than what was in my brain. There was no preparation. I was going to answer whatever questions he might have in my role as a clinician. 09:18:57 09:18:58 09:19:02 09:19:06 09:19:11

BY MS. CHACON: 09:19:12

Q So what questions did Dr. Trout have for you, Dr. Bressler, in the June 10th meeting? 09:19:12 09:19:16

A As I said, I recall being asked to tell him how I treat with anti-VEGF to patients, as I might explain to a patient for retinal diseases. 09:19:19 09:19:24 09:19:34

I recall answering his question about 09:19:37

what I know about viscosity when injecting an anti-VEGF drug, explaining -- 09:19:50 09:19:55

What I can recall is that I don't want the viscosity to be too great because if a needle is not placed properly on the syringe, it might pop off while we're trying to put it -- the medication inside the patient's eye. 09:20:10 09:20:12 09:20:15 09:20:18 09:20:21

And I recall in answering to his question about what volumes I would want to inject, to say we have experience with millions of injections by thousands of clinicians around the world using 0.5cc, so that ideally we would like our patients that we're injecting to be limited to 0.5cc. 09:20:24 09:20:35 09:20:35 09:20:38 09:20:42 09:20:48 09:20:53

Q What was your understanding as to why Dr. Trout was asking you these questions of why he was interested in them? 09:21:03 09:21:05 09:21:08

A I don't have an understanding. I presume he needed those perspectives to help form his declaration. 09:21:11 09:21:12 09:21:17

Q So he didn't explain the context as to why he was asking? 09:21:18 09:21:21

A He did not. 09:21:22

Q And, just to be clear, in your last 09:21:25

answer, you mentioned 0.5cc's. We're going to be 09:21:27

referring to various units of measurement here. 09:21:31

When you say "0.05," are you referring to -- is 09:21:34

that a way of saying microliters? Milliliters? I 09:21:39

want to make sure I understand what you mean by 09:21:44

"cc." 09:21:46

A Yeah. So it means half -- half of a 09:21:47

milliliter, 0.05ML. 09:21:53

Q 0.05ML? Okay. Thank you. 09:21:57

Was there anything else that Dr. Trout 09:22:03

asked you? 09:22:05

A Not that I can recall. 09:22:09

Q So in total, it sounds like he maybe 09:22:15

asked you two questions? Three questions? Does 09:22:18

that sound right? 09:22:20

MS. KAYALI: Objection. Foundation. 09:22:21

Vague. 09:22:25

You can answer. 09:22:25

THE WITNESS: I don't know how many 09:22:30

questions he asked, but I recall those three 09:22:31

topics. 09:22:34
BY MS. CHACON: 09:22:38
Q Aside from posing those three topics, is 09:22:38
there anything else that Dr. Trout said to you 09:22:54
during the June 10th call? 09:22:57
A I don't think so, other than 09:22:59
pleasantries and the good-bye. 09:23:00
Q So Dr. Trout didn't explain what 09:23:04
opinions he was formulating for this matter? 09:23:05
A He did not. 09:23:09
MS. KAYALI: Objection. Vague. 09:23:10
You can answer. 09:23:11
THE WITNESS: He did not. 09:23:14
BY MS. CHACON: 09:23:14
Q Now, leading up to the call with 09:23:14
Dr. Trout on June 10th, had you already formed 09:23:20
your opinions and prepared your declaration? 09:23:24
MS. KAYALI: Objection. Vague. 09:23:26
You can answer. 09:23:27
THE WITNESS: I had formed some of my 09:23:34
opinions. I hadn't finalized my declaration until 09:23:35
a week after our last conversation. 09:23:38

BY MS. CHACON: 09:23:40
Q How far along would you say that your 09:23:40
declaration was at the time that you talked to 09:23:43
Dr. Trout on June 10th? 09:23:45
MS. KAYALI: Objection. Vague. 09:23:47
You can answer. 09:23:48
THE WITNESS: I can't recall how far 09:23:55
along it was. 09:23:56
BY MS. CHACON: 09:23:57
Q Had you started writing your 09:23:57
declaration? 09:23:59
MS. KAYALI: Objection. Vague. 09:24:01
You can answer. 09:24:01
THE WITNESS: I had started writing my 09:24:02
declaration, to the best of my memory. I'm not 09:24:04
positive. 09:24:07
BY MS. CHACON: 09:24:07
Q And that would make sense; right? It 09:24:07
would be silly to get on a call with Dr. Trout and 09:24:10
explain your opinions if you hadn't already 09:24:13
started writing your declaration; right? 09:24:15
MS. KAYALI: Objection. Argumentative. 09:24:17

Lacks foundation. 09:24:18
You can answer. 09:24:19
THE WITNESS: I was prepared to answer 09:24:21
his questions with or without how much I had 09:24:22
already prepared for the declaration. 09:24:26
BY MS. CHACON: 09:24:28
Q Right. But knowing what your opinions 09:24:29
are and actually having memorialized them in some 09:24:32
degree, that would make sense before you would get 09:24:36
on a call with Dr. Trout; right? 09:24:39
MS. KAYALI: Objection. Foundation. 09:24:41
You can answer. 09:24:42
THE WITNESS: I don't think so. I 09:24:44
believe the information that he was asking me 09:24:45
about referred to my experience as a clinician. 09:24:51
BY MS. CHACON: 09:24:59
Q Okay. And just to make sure I 09:24:59
understand your answer, you had started working on 09:25:01
your declaration by the time the conversation had 09:25:04
on -- you had with Dr. Trout on June 10th; right? 09:25:07
A I think so, yes. 09:25:10
Q Okay. How would you go back to check to 09:25:12

make sure? 09:25:14

A I -- 09:25:19

MS. KAYALI: Objection. Vague. 09:25:20

You can answer. 09:25:21

THE WITNESS: I would have to turn to 09:25:22

the -- counsel and ask if I can see a copy of the 09:25:22

draft as it existed prior to June 12 or prior to 09:25:25

June 10. 09:25:29

BY MS. CHACON: 09:25:30

Q So let's turn to the second conversation 09:25:30

you had with Dr. Trout, which took place on 09:25:36

June 12th. And a similar question that I asked 09:25:38

you to the conversation on June 10th. 09:25:44

Was that meeting in-person or remotely? 09:25:46

A That, again, was remotely. 09:25:51

Q By Zoom? 09:25:53

A By Zoom. 09:25:55

Q What was the purpose of the second 09:25:56

meeting with Dr. Trout? 09:25:57

A That was to answer any additional 09:25:59

questions he might have having had the opportunity 09:26:00

to mull over the information I gave him during the 09:26:04

first meeting. 09:26:08

Q So is it your understanding that 09:26:09

Dr. Trout requested a second meeting with you? 09:26:11

A I don't recall who requested the second 09:26:16

meeting, it was not I. 09:26:20

Q Who participated in that second meeting 09:26:25

on June 12th? 09:26:28

A Again, in addition to Dr. Trout and 09:26:29

myself, I know Ms. Kayali was on the call, and 09:26:31

there may have been other lawyers from 09:26:37

Williams & Connolly on the call. That, I cannot 09:26:39

recall. 09:26:42

Q How long did the June 12th meeting last 09:26:43

for? 09:26:45

A That was shorter. That was perhaps 09:26:47

about 15 minutes. 09:26:51

Q What did you and Dr. Trout discuss? 09:26:58

A I can't recall the details of that 09:27:02

second one except I was ready and willing and able 09:27:03

to answer any questions he had. 09:27:06

Q Do you have any recollection if it was 09:27:10

related to the subject matter that you already 09:27:11

spoke to him about on June 10th? 09:27:14

MS. KAYALI: Objection. Vague. 09:27:17

You can answer. 09:27:18

THE WITNESS: I believe it was about the same topics with further clarification of questions, but I would not be able to tell you what those additional clarifying questions were. 09:27:23 09:27:23 09:27:26 09:27:29

BY MS. CHACON: 09:27:32

Q And, to be clear, did you have any questions for Dr. Trout in that June 12th meeting? 09:27:32 09:27:39 09:27:41

A I did not have any questions for him. 09:27:43

Q So June 12th is about a week before your final declaration was submitted on June 19th; is that right? 09:27:57 09:28:02 09:28:04

A That is correct. 09:28:05

Q And how far along would you say that your declaration was as of June 12th? 09:28:06 09:28:08

MS. KAYALI: Objection. Vague. 09:28:11

THE WITNESS: It's hard to talk about how far along it was. Again, there were drafts that I was working on at that time. 09:28:14 09:28:15 09:28:19

BY MS. CHACON: 09:28:21
Q But you had formed your opinions by 09:28:21
June 12th. 09:28:27
Is that fair to say? 09:28:28
MS. KAYALI: Objection. Vague. 09:28:29
THE WITNESS: I don't think that would 09:28:32
be fair to say, because I was forming my opinions 09:28:32
through much of the time up until near the end of 09:28:37
the week of June 19th. 09:28:44
BY MS. CHACON: 09:28:46
Q Okay. So you were forming your opinions 09:28:46
up until the final declaration was executed on 09:28:48
June 19th? 09:28:52
MS. KAYALI: Objection. Vague. 09:28:53
THE WITNESS: I would state that most of 09:28:58
my opinions were already formed prior to the date 09:29:01
of June 19, when just editorial revisions were 09:29:05
being made. 09:29:16
BY MS. CHACON: 09:29:17
Q Okay. And were most of your opinions 09:29:17
formed before you spoke with Dr. Trout on 09:29:19
June 10th and June 12th? 09:29:23

MS. KAYALI: Objection. Vague. 09:29:25

THE WITNESS: I couldn't characterize 09:29:30

when all my opinions that are in this declaration 09:29:31

were formed relative to those meetings. 09:29:34

BY MS. CHACON: 09:29:41

Q Now, after the submission of your 09:29:41

declaration on June 19th, did you have any other 09:29:51

communication with Dr. Trout? 09:29:55

A I did not. 09:29:58

Q Did you review Dr. Trout's declaration 09:30:13

in preparation for your deposition today? 09:30:15

A I did not. 09:30:18

Q Have you seen or ever reviewed 09:30:19

Dr. Trout's declaration? 09:30:21

A I have not seen or reviewed his 09:30:23

declaration. Correct. 09:30:26

Q Was there any information that Dr. Trout 09:30:34

told you that you are relying on in forming your 09:30:36

opinions in your declaration? 09:30:41

A As I said before, I did not ask him any 09:30:45

questions. There was no information that I was 09:30:48

obtaining from him to form my opinions that are in 09:30:53

my declaration. 09:30:56

Q Okay. So any discussion in your 09:30:57

declaration about formulation or viscosity -- that 09:30:59

comes from you and not Dr. Trout; correct? 09:31:03

MS. KAYALI: Objection. Foundation. 09:31:06

You can answer. 09:31:09

THE WITNESS: The opinions I have on 09:31:14

formulation as it deals with viscosity or volume 09:31:16

are any opinions without any input or knowledge 09:31:21

from Dr. Trout. Correct. 09:31:25

BY MS. CHACON: 09:31:26

Q And we've talked a little bit already 09:31:26

about sort of the drafting process in the course 09:31:39

of this last discussion. I want to dig a little 09:31:42

deeper than that. 09:31:48

So can you describe to me at a high 09:31:49

level without revealing any communications you had 09:31:51

with counsel just generally what the process was 09:31:53

for you preparing your declaration. 09:31:55

MS. KAYALI: And, again, I'll caution 09:31:57

the witness not to reveal the substance of any 09:31:59

attorney-client communications. 09:32:01

But you can answer without doing so.
THE WITNESS: I had extensive discussions about the matter contained followed by receiving an initial draft of a declaration at which I started to heavily edit areas that dealt with clinical research or a clinician.
Thereafter, there were parts going back and forth -- questions and answers to clarify it, all leading to the final draft that we have here.
BY MS. CHACON:
Q When you say you had extensive discussions about the matter followed by receiving an initial draft, of the approximately 60 or so hours that you estimated working on this matter, approximately how much of that time was dedicated to those discussions before receiving an initial draft?
MS. KAYALI: Objection. Vague.
THE WITNESS: Before receiving the initial draft, those hours included reviewing exhibits that were provided to me along with discussions of the matter contained.

BY MS. CHACON: 09:33:37

Q Okay. And those discussions that 09:33:37

happened with counsel, how much time did you spend 09:33:39

doing that before receiving an initial draft? 09:33:43

MS. KAYALI: Objection. Vague. 09:33:46

THE WITNESS: I would estimate 10 09:33:51

hours. 09:33:53

BY MS. CHACON: 09:33:54

Q Now, you mentioned, when you received an 09:33:54

initial draft, that you did some editing to 09:34:03

certain portions of the declaration. Is that 09:34:06

accurate? 09:34:10

MS. KAYALI: Objection. Foundation. 09:34:11

You can answer. 09:34:12

THE WITNESS: I said extensive editing. 09:34:18

In my experience as an editor and my experience in 09:34:20

writing many peer-reviewed medical literature 09:34:25

papers, I do very extensive editing often when I 09:34:28

get information on clinical research or clinical 09:34:35

items. 09:34:43

THE STENOGRAPHER: "Or clinical..." 09:34:43

THE WITNESS: "Items." 09:34:47

BY MS. CHACON: 09:34:48

Q Now, the reason for significant 09:34:48

editing -- is that because you didn't agree with 09:34:51

anything that was being provided to you? 09:34:54

MS. KAYALI: Objection. Foundation. 09:34:57

Again, I'll caution you not to reveal 09:34:58

the substance of any attorney-client 09:35:01

communications, which would include the content of 09:35:03

drafts. 09:35:07

THE WITNESS: It could be clarifying 09:35:10

information that I thought was a more clear, 09:35:12

precise way of describing the content. 09:35:17

Occasionally, it could be where I thought there 09:35:19

was a different interpretation of the results, for 09:35:25

example, of a clinical trial. 09:35:31

BY MS. CHACON: 09:35:33

Q If you could turn back to your Table of 09:35:33

Contents in your declaration, Dr. Bressler, I'd 09:35:39

like to get a better sense of some of the sections 09:35:42

in particular that you did extensive editing to. 09:35:45

Is there any particular section in your 09:35:49

Table of Contents that you could point me to where 09:35:51

you did extensive editing? 09:35:53

MS. KAYALI: Objection. Foundation. 09:35:56

Vague. 09:35:58

You can answer. 09:35:58

THE WITNESS: It's very difficult. I 09:36:04

would have to go through most of the clinical 09:36:05

information that begins with the state of the art 09:36:07

as of May 2018 through the end of my conclusion. 09:36:09

I can tell you that I did very little, 09:36:14

if any, editing to the legal standards for the 09:36:17

'036 patent or the claim construction. 09:36:23

BY MS. CHACON: 09:36:27

Q Was there any portion of your 09:36:27

declaration, Dr. Bressler, that you drafted in the 09:36:30

first instance? 09:36:32

MS. KAYALI: Objection. Vague. 09:36:33

THE WITNESS: Could you repeat the 09:36:41

question. 09:36:41

BY MS. CHACON: 09:36:41

Q Was there any portion of your 09:36:41

declaration that you drafted in the first 09:36:43

instance? 09:36:45

MS. KAYALI: Objection. Vague. 09:36:49
You can answer. 09:36:50
THE WITNESS: The portions that I would 09:36:55
edit or clarify were words that I wrote down first 09:36:56
on a draft that I had been handed. 09:37:01
BY MS. CHACON: 09:37:04
Q And just sort of going back to the 09:37:04
process, you had mentioned that there was kind of 09:37:32
some back and forth in answering questions. 09:37:35
I guess just approximately how many 09:37:43
versions or drafts did you end up reviewing and 09:37:44
editing? 09:37:48
MS. KAYALI: Objection. Foundation. 09:37:49
Vague. 09:37:51
THE WITNESS: I would estimate 09:37:57
perhaps 30 to 40 drafts, maybe more. 09:38:02
BY MS. CHACON: 09:38:09
Q So you reviewed 30 or 40 drafts between 09:38:09
sometime in May of 2026 and June 19th, 2026? 09:38:21
A That is correct. It sometimes might 09:38:28
include just a small portion that was getting 09:38:31
edited. It might include, in the beginning, 09:38:34

looking through the entire draft. 09:38:37

Q And we'll talk in a moment about sort of your -- I'll say your day job, but I suspect that you're a very busy man. 30 to 40 drafts seems like a lot. 09:39:06 09:39:08 09:39:11 09:39:16

How did you find the time to do all of that? 09:39:17 09:39:19

MS. KAYALI: Objection. Argumentative. 09:39:19

THE WITNESS: Working extensively on reviewing manuscripts and drafts all the time in the clinical literature, and this is similar. 09:39:27 09:39:29 09:39:32

I have enough time to be able to do that in the hours that were devoted to this, again, emphasizing that some of those drafts may have been just to review a paragraph that was revised based on discussions, and that might take very little time, whereas other portions might take hours to review. 09:39:37 09:39:41 09:39:48 09:39:51 09:39:53 09:39:57 09:40:00

MS. KAYALI: Counsel, I don't want to interrupt a line of questions, but at some point I could probably use a break. 09:40:26 09:40:28 09:40:31

MS. CHACON: No. You're reading my 09:40:33

mind. I was just about to suggest to Dr. Bressler that we've been going for about an hour and a half. 09:40:34 09:40:37 09:40:39

Would you like to take a break? 09:40:39

THE WITNESS: I would. 09:40:41

MS. CHACON: Okay. Great. 09:40:42

THE WITNESS: Thank you. 09:40:44

THE VIDEOGRAPHER: We are going off the record. The time is 9:40. 09:40:45 09:40:46

(Recess.) 09:40:48

THE VIDEOGRAPHER: We are going back on the record. The time is 9:54. 09:54:55 09:54:56

BY MS. CHACON: 09:54:59

Q Dr. Bressler, we're going to turn to your declaration, which we -- is marked to the proceeding as 2052 -- Exhibit 2052. 09:54:59 09:55:02 09:55:06

And I understand in Section 2 of your declaration, you provide a summary of your qualifications and experience; is that right? 09:55:09 09:55:13 09:55:16

A That is correct. 09:55:17

Q Now, I -- it's quite long, so I won't -- we're not going to go through it all in detail, 09:55:18 09:55:23

but what I really want to get down to is your treatment of patients. Okay? 09:55:25 09:55:30

And earlier you mentioned that you've been treating patients or working in this field for over 40 years; is that right? 09:55:32 09:55:35 09:55:37

A That is correct. 09:55:40

Q Okay. Can you just at a high level describe for me what your current practice looks like in terms of treating patients? 09:55:41 09:55:48 09:55:51

A My current practice for treating patients includes approximately one day a week of about 26 to 30 patients, all of whom have retinal disease. 09:55:52 09:55:54 09:56:01 09:56:09

Q So within a week, you see approximately 26 to 30 patients; right? 09:56:14 09:56:16

A At this time currently. 09:56:19

Q Okay. And of those -- I'm just going to say 30 just to make it a round number. Of those 30 patients that you see that have retinal diseases, approximately how many are you administering an anti-VEGF intravitreal injection? 09:56:21 09:56:24 09:56:27 09:56:30 09:56:34

A Approximately 10 each week. 09:56:42

Q Okay. We're going to turn back to that in just a second. Now, you mentioned that your current practice is about 30 patients a week. 09:56:55 09:56:55 09:56:57

Is that more or less than your prior practice? I'm just trying to get a sense of, you know, what your current practice looks like as compared to prior treating practice. 09:57:02 09:57:06 09:57:09 09:57:11

A It's less. A year or so ago, there might have been 20 percent more. Prior to that, 10 years ago, it would be three full days a week. 09:57:14 09:57:17 09:57:26 09:57:29

And initially when I started it was four full days a week, and those would consist of anywhere from 25 to 45 patients in a day. 09:57:34 09:57:36 09:57:38

Q Okay. So let's rewind back to about 10 years ago, which was 2016. So you understand, Dr. Bressler, that the -- the priority date or the critical date that we're talking about in this proceeding is May 2018? 09:58:01 09:58:06 09:58:11 09:58:14 09:58:17

Do you understand that? 09:58:19

A I do understand that. 09:58:19

Q Okay. So as of May 2018, can you 09:58:22

describe to me what your treating practice looked like? 09:58:26 09:58:28

A In 2018 it was likely two and a half days a week. The full days would be approximately 40 patients, on average, and the half day would be approximately 20 patients on average. 09:58:30 09:58:34 09:58:42 09:58:45

Q So about a hundred patients a week on average? 09:58:48 09:58:51

A On average about a hundred patients a week. 09:58:51 09:58:54

Q And at that time the hundred patients a week that you saw -- did they all have retinal diseases? 09:58:58 09:59:02 09:59:05

A At that time, 99 percent had retinal diseases. 09:59:07 09:59:10

Q Okay. So in 2018, describe for me, if you will, your personal armamentarium of treatments that you would use on the 99 or so retinal patients that you were seeing. 09:59:11 09:59:31 09:59:40 09:59:42

MS. KAYALI: Objection. Vague. 09:59:46

You can answer. 09:59:47

THE WITNESS: The armamentarium included 09:59:55

anti-VEGF injections, laser to the retina, rarely photodynamic therapy to the retina. 10:00:00 10:00:13

BY MS. CHACON: 10:00:29

Q Is it fair to say, then, that for the vast majority of the hundred or so patients a week you were seeing in 2018, that most of them were receiving an anti-VEGF injection for treatment? 10:00:29 10:00:31 10:00:36 10:00:39

A It would be fair to say, among those hundred, if they needed treatment, most of the treatments were anti-VEGF treatments. 10:00:44 10:00:47 10:00:49

Q At that time what anti-VEGF treatments were you utilizing with your patients? 10:00:53 10:00:56

A Typically I would use aflibercept 2-mg. Occasionally, I would use ranibizumab 0.5-mg. And less commonly I would use repackaged or compounded bevacizumab. 10:01:00 10:01:10 10:01:21 10:01:23

Q Why were you using aflibercept more often than ranibizumab or off-label bevacizumab. 10:01:29 10:01:34

A The DRCR network had published a head-to-head trial comparing aflibercept 2-mg with ranibizumab and found that when the vision was moderately impaired or even worse, the aflibercept 10:01:41 10:01:44 10:01:49 10:01:55

was superior.

In all other instances, there was no evidence that one agent was superior to the other. There was no evidence that one agent was safer than the other. There was no evidence that one agent was more durable than the other.

And so a third of the treatments would be in diabetic macular edema. And rather than having more than one agent to have to deal with, it was preferable to just stick with aflibercept for most of the patients.

For those in whom it was superior, as in diabetic macular edema, and where there was one that wasn't superior than the other, there was no reason to stock or consider or order another agent. There might be an error when you're trying to remember more than one to do.

So it's easier -- it facilitated more efficiently than all those other diseases to use the one agent that had shown to be superior. Bevacizumab was not shown to be superior to those, and in some instances inferior in

treatment.

And so it was preferred to reserve that if finances of the patient -- their personal finances, their insurance precluded their likely ability to be able to afford ranibizumab or aflibercept. 10:03:22 10:03:22 10:03:24 10:03:28 10:03:33 10:03:35

Q Now, you mentioned superiority. Can you describe to me what you mean by that in your response? I'm not quite sure what you mean by being superior. 10:03:41 10:03:45 10:03:47 10:03:50

MS. KAYALI: Objection. Vague. 10:03:53

You can answer. 10:04:02

THE WITNESS: By superior, I mean the visual acuity outcomes of using aflibercept 2 mg versus ranibizumab. 10:04:03 10:04:05 10:04:09

And it was shown at one year and over two years that the visual acuity outcomes on average as well as the percentage of individuals who gained 10 or more letters compared to where they started was greater confidently in the aflibercept set group compared with the ranibizumab group. 10:04:13 10:04:16 10:04:23 10:04:25 10:04:29 10:04:38 10:04:40

BY MS. CHACON: 10:04:44

Q I see. And the reason why I'm asking 10:04:44

is -- and I'm sure you're familiar with this, 10:04:46

Dr. Bressler. In, for example, the FDA context; 10:04:49

right? "Superior" has -- is a certain term of 10:04:53

art; right? A superiority study versus a 10:04:57

non-inferiority study. 10:04:59

So when you say "superior," what I heard 10:05:03

you just say is the data was showing it greater. 10:05:07

Am I understanding you correctly? 10:05:10

MS. KAYALI: Objection. Foundation. 10:05:12

Vague. 10:05:13

THE WITNESS: I'll try to clarify by 10:05:18

saying the average number of letters gained if you 10:05:19

use aflibercept or the percentage of individuals 10:05:22

who gained two or more lines on a standard eye 10:05:26

chart were greater in the aflibercept group than 10:05:30

in the ranibizumab group in certain instances of 10:05:35

diabetic macular edema. 10:05:41

BY MS. CHACON: 10:05:41

Q Was it statistically significantly 10:05:41

greater? Do you recall? 10:05:44

MS. KAYALI: Objection. Foundation. 10:05:46

THE WITNESS: As a prespecified outcome 10:05:54
of the trial that showed the superiority, it was 10:05:54
statistically significant and clinically relevant. 10:05:56
BY MS. CHACON: 10:06:00
Q What do you mean by "clinically 10:06:00
relevant"? 10:06:05
MS. KAYALI: Objection. Vague. 10:06:06
You can answer. 10:06:07
THE WITNESS: When we look at the 10:06:14
history of improvement in vision that 10:06:15
ophthalmologists judge are relevant to the 10:06:18
patient's day-to-day function, having at 10:06:23
least 10 percent of the people in one 10:06:32
group -- 10 percent more in one group gaining 10 10:06:34
or more letters is considered a relevant benefit 10:06:39
for the patient, not just a statistically 10:06:45
significant difference if that's how the study was 10:06:50
designed. 10:06:54
BY MS. CHACON: 10:06:54
Q Now, is that 10 percent metric that you 10:06:54
just mentioned -- is that in a guidance somewhere? 10:07:00

Does that come up -- derive from a study? 10:07:07

Where does that number come from? 10:07:10

MS. KAYALI: Objection. Foundation. 10:07:12

Vague. 10:07:13

THE WITNESS: For example, when trials 10:07:14

are being designed for non-inferiority in retinal 10:07:21

diseases, that has been an agreed-upon minimum 10:07:27

that is likely a real difference to the patient's 10:07:31

day-to-day function. 10:07:38

BY MS. CHACON: 10:07:40

Q Are there any other metrics that are 10:07:40

considered in such clinical trials to assess the 10:07:43

impact on a patient's day-to-day function? 10:07:47

A The average change in vision for each 10:07:55

group and the percentage that lose 10 or more 10:07:57

letters or 2 or more lines of vision on a standard 10:08:00

eye chart. 10:08:03

Q Anything else? 10:08:12

A None that I can think of at this time. 10:08:13

Q Now, you were talking about a DRCR 10:08:23

network study. Do you recall exactly what study 10:08:26

that was? 10:08:29

A That was the DRCR retina network protocol T. 10:08:31 10:08:34

Q Protocol T? Okay. And I believe you're an author in one of those papers; correct? 10:08:36 10:08:46

A I am an author on that paper. It was published in the New England Journal of Medicine. 10:08:49 10:08:51

Q Were you the principal investigator of that study? 10:08:57 10:08:59

A I was the principal investigator of the chair's office as that study was being designed. I remained chair for seven years. 10:09:00 10:09:02 10:09:06

And as we transitioned to a new chair, I was the past chair of the chair's office for that study when it was then published in 2015. 10:09:08 10:09:12 10:09:15

Q Okay. So thank you for the explanation in terms of -- I believe the original question was directed to why you chose to use aflibercpet over ranibizumab and off-label bevacizumab for your patients. 10:09:24 10:09:26 10:09:30 10:09:33 10:09:36

Now, turning to ranibizumab and bevacizumab for a moment, what would be the circumstances in which you would have utilized 10:09:38 10:09:45 10:09:47

those treatments for a patient over aflibercept? 10:09:51

A For ranibizumab, if the patient's 10:09:59

insurance would only cover that and not 10:10:03

aflibercept, it's far better to use ranibizumab 10:10:07

than anything else in those circumstances. 10:10:12

In addition, prior to aflibercept being 10:10:17

available, if someone was being treated with 10:10:22

ranibizumab and having an excellent result and 10:10:25

maintaining an excellent result as they continue 10:10:25

to receive that periodically, I would not be able 10:10:34

to think of a reason to switch them to another 10:10:37

anti-VEGF agent. 10:10:41

Q Were there any safety concerns with 10:10:44

aflibercept that would have caused you to utilize 10:10:49

ranibizumab or off-label bevacizumab for a patient 10:10:52

in your practice? 10:10:56

A There were no safety concerns comparing 10:10:57

aflibercept 2 mg with ranibizumab for the patient. 10:11:01

Q And what about as compared to 10:11:07

bevacizumab? 10:11:10

A There are greater concerns about using 10:11:11

the bevacizumab because it goes through additional 10:11:15

steps of repackaging and compounding. That allows additional steps where infection might occur. 10:11:18 10:11:21

Q So I want to get a better sense. Pretend I'm one of your patients in 2018. I'm going into your office for an intravitreal injection. 10:11:32 10:11:34 10:11:38 10:11:41

Walk me through your process of preparing a patient and administering the drug. 10:11:42 10:11:43

A I would first discuss with the patient and show images of the condition of their retina. I would then explain the risks and benefits of not treating it, treating it with aflibercept, treating it with other agents. 10:11:53 10:11:54 10:12:01 10:12:06 10:12:12

I would explain to them why I was choosing a particular agent to treat them. Let's say they had diabetic macular edema with at least moderate vision impairment. 10:12:13 10:12:17 10:12:20 10:12:24

I would explain to them that this aflibercept 2 mg agent is superior to the other agents available to us and your insurance will cover that. And so I would like to begin to do that. 10:12:27 10:12:29 10:12:31 10:12:35 10:12:38

I then would tell them typically I need to follow them monthly for the next two years. I may not need to treat them monthly, but I need to monitor them monthly and that at each of those monthly visits, I'll make a decision with them whether treatment is indicated. 10:12:41 10:12:46 10:12:50 10:12:53 10:12:57 10:13:01

And for initial set of months, I'm going to treat them sort of as a loading dose, and then I will answer their questions about the logistics of all of that. 10:13:03 10:13:06 10:13:15 10:13:17

Following that, I would go through what the risks are in doing that, including the rare risk of infection that it would give them pain on a scale of 1 to 10, maybe a 9 or 10, and to please contact us promptly. 10:13:19 10:13:23 10:13:29 10:13:34 10:13:39

And otherwise, that it's likely that they will have irritation because we put antiseptic on the surface of the eye to try to avoid an infection and that that antiseptic may make their eye feel scratchy, like there's sand in it, for the next day or so. And that they may see a dot of blood on the white part of their eye 10:13:42 10:13:44 10:13:46 10:13:50 10:13:57 10:14:01 10:14:05

following the injection, and that's like a black and blue mark and is likely just to resolve over the next week or so. 10:14:08 10:14:11 10:14:14

They may see floaters from the injection itself or from some changes to the vitreous content following the injection. 10:14:15 10:14:18 10:14:22

And those typically go away, but if they have any other concerns or changes in their vision, they should contact us promptly so we could check to see what would be the cause for any change in vision before I see them back a month later. 10:14:27 10:14:28 10:14:32 10:14:35 10:14:38 10:14:40

Q So just to recap a couple of the risks or concerns that you would flag for them, you might flag risk of infection is one I understood. Like endophthalmitis, am I understanding, is that a risk of infection? 10:14:55 10:15:00 10:15:03 10:15:07 10:15:14

A Correct. Yes. 10:15:15

Q Okay. And you would also advise or warn about irritation because of antiseptic that would be put on the needle; is that correct? 10:15:16 10:15:18 10:15:21

A Not correct. I would warn them about 10:15:23

the irritation because of the antiseptic placed on the surface of the eye -- 10:15:26 10:15:29

Q Okay. 10:15:31

A -- to try to get rid of all of the bacteria before the injection. 10:15:32 10:15:35

Q Okay. Thank you for that correction. 10:15:39

And you mentioned that you had also advised them or warned them that they could see changes in vision or have floaters as part of the injection; is that right? 10:15:40 10:15:45 10:15:48 10:15:51

A That is correct. 10:15:53

Q Okay. Are there any other safety concerns that you would typically warn your anti-VEGF-receiving patients before injection? 10:15:54 10:15:57 10:16:00

A If the patient is pregnant or contemplating pregnancy, in those rare instances, I would go through the risks and benefits of considering treatment versus the potential unknown risk to a fetus indicating that we have no evidence that there's any risk to the fetus. 10:16:09 10:16:11 10:16:14 10:16:17 10:16:22 10:16:26

I would explain to them what to anticipate in terms of pain during the injection 10:16:33 10:16:35

because there typically is anxiety the first time over hearing that you're going to put a needle into the middle cavity of someone's eye. 10:16:38 10:16:44 10:16:47

And I would explain that we typically just use topical anesthetic to minimize discomfort, that we use a needle about the size of a hair so that it's likely to minimize discomfort. 10:16:50 10:16:52 10:16:56 10:16:58

And that they will feel some pain, hopefully for less than a second, while the treatment is going on, and I will try to walk them through that, and please try to get through the first one so we can try to save your vision. 10:17:02 10:17:04 10:17:07 10:17:10 10:17:13

And then it will be much easier once they experience that first injection, because then they know what it is. 10:17:15 10:17:18 10:17:25

Q Okay. Now you've given the patient warnings or precautions before the injection. Walk me through how you actually prepare or were preparing an injection of 2 mg EYLEA in 2018. 10:17:25 10:17:28 10:17:31 10:17:33

A I cannot recall at that time whether the prefilled syringe was available or not. If it was available, our division started using it within a 10:17:44 10:17:46 10:17:50

year after it was available, so I would have to look up when it became available, but prior to that we would have a vial. 10:17:54 10:17:57 10:17:59

And we would order the medication, and we would have a technician remove that from a refrigerated area and bring it to a room where we would do the injection. 10:18:06 10:18:08 10:18:13 10:18:13

The patient would review a written informed consent that went over what I just told them, and we would each sign the consent. I would walk into the room. 10:18:17 10:18:20 10:18:22 10:18:28

I would take out the aflibercept vial from the box myself. I would confirm that it has no particulate matter or other abnormal appearance other than a clear vial of solution. 10:18:30 10:18:33 10:18:36 10:18:42

I would take a syringe that has gradations as a 1-milliliter syringe down to .1, .2, .3, .4 in that syringe and look at where .05 is on the syringe. 10:18:47 10:18:55 10:19:00 10:19:15

I would take a cap off of the vial. I would use a 19-gauge filter needle to go into the vial in a sterile manner and pull up the solution. 10:19:15 10:19:18 10:19:22

I would then cap that and put that aside. 10:19:29

I then would begin to numb the patient 10:19:31
after telling them we're doing the right eye, if 10:19:34
that's what we're doing, with either EYLEA or 10:19:40
aflibercept -- whichever word I used for that. 10:19:42
They would agree. 10:19:45

And I would then, over their right eye, 10:19:46
put in numbing drops. I would then put in a drop 10:19:50
of antiseptic to begin to kill bacteria and hope 10:19:54
that it would tell me that the anesthetic is 10:19:59
working because otherwise that would burn 10:20:01
terribly. 10:20:04

I would then put additional antiseptic 10:20:04
on the lids and lashes so that any bacteria there 10:20:07
might be killed. 10:20:10

I would then take a pediatric lid 10:20:11
speculum to separate the lids so that I don't have 10:20:11
to worry about their blinking in the way of what 10:20:15
I'm trying to do. 10:20:21

I would then take a Q-Tip and put some 10:20:22
additional anesthetic on it and press on the eye 10:20:25
to try to reduce the volume inside of the eye 10:20:28

because we want to not raise the pressure substantially, even when we're putting in this just this .05-milliliter. 10:20:31 10:20:35 10:20:37

I would mark three and a half millimeters from the edge of the cornea to the sclera as to where I wanted to inject. 10:20:42 10:20:45 10:20:49

I would then take the needle and -- and syringe that I prepared, remove the 19-gauge needle, put a 30-gauge needle on, clear the fluid up to getting all the air out and getting it up to .05-milliliter. 10:20:53 10:20:57 10:21:00 10:21:04 10:21:06

I would then take another Q-Tip in hand if I needed it to position the eye, but I would have them look up and to the left if it was their right eye. 10:21:11 10:21:15 10:21:18 10:21:21

And in that area, I would inject with the needle almost up to the hub of the needle -- it's a short 30-gauge needle -- towards the direction of the optic nerve, insert the solution fairly promptly, remove it, put the Q-Tip on it, take the lid speculum out, put a tissue on, and tell them if everything went well, that everything 10:21:22 10:21:24 10:21:27 10:21:29 10:21:33 10:21:37 10:21:39

went well. 10:21:42

After about a minute, I would have them open their eyes. I would check that they can see my hand movement. 10:21:43 10:21:45 10:21:48

And, as long as they could, I would be convinced that the pressure was not compromised for their particular optic nerve or eye. 10:21:50 10:21:52 10:21:56

And I would sit them up, make sure that they don't faint, and then I would have them on their way, reminding them all the time about what to look for for endophthalmitis and that I need to see them every month for the next two years. 10:21:58 10:22:01 10:22:04 10:22:07 10:22:10

Q Okay. A couple of follow-up questions for you on that. Thank you for the detailed overview. That's very helpful. 10:22:17 10:22:18 10:22:20

You had mentioned that, prior to the injection, that you push on the eye to reduce the volume, I think I heard you say. 10:22:23 10:22:26 10:22:29

A The volume of the vitreous. 10:22:31

Q The volume of the vitreous. Why do you do that? 10:22:33 10:22:36

A Because we want to reduce the total 10:22:37

volume that's in the vitreous. By adding this .05-milliliter, it might increase the pressure inside of the eye. 10:22:39 10:22:42 10:22:47

And, in some people, if their optic nerve is so predisposed, that might cause damage to their optic nerve or it might interfere with the blood flow of the retinal artery, which then would not perfuse to the retina. 10:22:48 10:22:52 10:22:55 10:22:59 10:23:03

And that's why we try to reduce the volume to a small amount of the vitreous by pressing on it for about 30 seconds in total. 10:23:03 10:23:05 10:23:09

Q So this is going to sound very naive of me, but when you push on the vitreous, does liquid come out, or what is actually happening when you're pushing on the vitreous? 10:23:17 10:23:22 10:23:26 10:23:28

A Excuse me. Yeah. So this is before the injection is done. So it's a closed system as if you're pressing on your eyeball, you're rubbing your eye. 10:23:29 10:23:32 10:23:35 10:23:39

So it's pressing in a small spot on the sclera with a Q-Tip, and that compression is going to hopefully deterges or remove some volume of the 10:23:40 10:23:43 10:23:48

vitreous. 10:23:55

Q So when you say it removes the volume of 10:23:55

the vitreous, does that literally mean that there 10:23:58

is some liquid coming out of the sclera? 10:24:00

A Yeah. It does not -- 10:24:03

MS. KAYALI: Objection. Vague. 10:24:05

You can answer. 10:24:06

THE WITNESS: It does not come -- it 10:24:07

does not come out by pressing on there. The 10:24:08

volume in total inside the vitreous is probably 10:24:13

diffusing through other parts of the eye. 10:24:18

BY MS. CHACON: 10:24:22

Q I see. Okay. Now, you mentioned that 10:24:22

after the injection, you wave your hand in front 10:24:29

of the person's -- you know, to see if they can 10:24:33

see your hand; right? 10:24:36

A That is correct. 10:24:38

Q And the reason for that is so that you 10:24:39

can tell whether or not they're exhibiting any 10:24:41

issues with pressure. 10:24:43

Did I understand that correctly? 10:24:45

MS. KAYALI: Objection. Foundation. 10:24:46

Vague. 10:24:48

You can answer. 10:24:48

THE WITNESS: The reason I'm doing it is to make sure that, by adding this additional volume inside of the eye, it has not compromised the flow through the essential retinal artery. 10:24:50 10:24:51 10:24:54 10:24:57

BY MS. CHACON: 10:25:03

Q Okay. And if you had a patient who could not see your hand waving, what would you do? 10:25:04 10:25:07

A I would not have them leave at that point. I would say, "Why don't you wait in this other room, and let's see if the circulation returns." 10:25:12 10:25:14 10:25:17 10:25:21

But I would do that only after I take a look to the back of the eye to see if I see pulsations of the artery, which would imply that, whatever pressure was inside of the eye was compromising the flow so that the artery was pulsating or to see if perhaps there was no blood flow for the artery at all. 10:25:22 10:25:24 10:25:27 10:25:31 10:25:34 10:25:38 10:25:42

Q Now, is any issue with blood flow -- is that always related to intraocular pressure 10:25:44 10:25:48

increases, or are there other reasons why there could be a decrease in blood flow? 10:25:53 10:25:56

MS. KAYALI: Objection. Vague. 10:25:59

You can answer. 10:26:00

THE WITNESS: In the scenario where you have just injected someone, it's almost certainly going to be due to increasing the pressure inside of the eye. 10:26:01 10:26:02 10:26:07 10:26:09

I could hypothesize that maybe if someone had a heart attack right during the injection, to compromise their heart blood flow, that could be a reason, but, again, it's almost certainly going to be because the pressure was increased. And that affected the ability of the central retinal artery to perfuse the retina. 10:26:10 10:26:13 10:26:16 10:26:24 10:26:25 10:26:28 10:26:30

BY MS. CHACON: 10:26:34

Q Okay. So for a patient who is experiencing the concern about not being able to see your hand after the injection, how long do they typically stay in post-op under your care? 10:26:34 10:26:37 10:26:39 10:26:44

A You have to understand that this almost never has happened to me. I check, nevertheless, 10:26:48 10:26:51

because maybe I did not press on the eye as much as I thought I should have, but it has happened. 10:26:57 10:27:00

And it's been transient in the level of one to four minutes of some impaired flow that is getting better every minute with the vision improving every minute. 10:27:03 10:27:08 10:27:12 10:27:16

Q I see. So for patients who don't have that concern where you give the injection, and then they sit up and they're fine, how long are they typically staying in your office before they're on their way? 10:27:17 10:27:22 10:27:26 10:27:29 10:27:32

A As long as it takes them to get to our front desk area, which is down the hallway, to check out and perhaps make their next appointment. 10:27:36 10:27:42 10:27:46

Q Okay. And so just to go back to the pre-procedure for a moment. When you're pressing a Q-Tip against the -- 10:27:49 10:27:55 10:27:58

(Simultaneous speakers.) 10:28:01

BY MS. CHACON: 10:28:01

Q No. Thank you for the correction. Let me restart the question again so we get it right. Okay? 10:28:01 10:28:04 10:28:07

When you are in the pre-procedure and you're pressing a Q-Tip against the sclera to reduce the volume prior to injection, is that a way to mitigate -- increase ocular pressure? 10:28:07 10:28:10 10:28:14 10:28:19

MS. KAYALI: Objection. Vague. 10:28:26

You can answer. 10:28:28

THE WITNESS: It's a way to make it less likely that after injecting the anti-VEGF agent that there will be elevated pressure that could interfere with the perfusion of the retinal artery. 10:28:33 10:28:34 10:28:42 10:28:45 10:28:49

BY MS. CHACON: 10:28:50

Q All right. So let's go back to the volume of patients that you were seeing in 2018. So you mentioned around that time you were approximately seeing about 100 patients a week. 10:28:50 10:29:07 10:29:09 10:29:11

Is it fair to extrapolate that out and say, you know, in 2018, you probably saw roughly 5,000 patients that year or maybe I should say visits? 10:29:16 10:29:18 10:29:21 10:29:24

A I would multiply it by between 30 and 40 weeks because of all the other activities I do in 10:29:27 10:29:31

my job. 10:29:35

Q Sure. 10:29:36

A I might be away for various business reasons related to the clinical research or other educational activities. 10:29:37 10:29:39 10:29:44

Q That's fair. And so is it, I guess, a better estimate to say about 3- to 4,000 visits in 2018? 10:29:48 10:29:50 10:29:53

A 100 times 30. 3,000. Yes. 10:30:04

Q And you said roughly 99 percent of the patients you see in a week were receiving an intravitreal injection or an anti-VEGF; is that right? 10:30:09 10:30:11 10:30:13 10:30:19

A I shook my head no there because the second part of your question as I understood was a correction to it. So if you can just repeat it, then I'll answer it again. 10:30:21 10:30:24 10:30:28 10:30:30

Q Sure. I think I previously understood you to say that 99 percent had retinal diseases of the 100 patients you saw per week, and the vast majority of those were receiving an anti-VEGF injection; is that right? 10:30:32 10:30:34 10:30:39 10:30:44 10:30:49

A I would say that approximately 10 to 15 of the patients each day of the 40 patients were receiving anti-VEGF injections -- 10:30:50 10:31:00 10:31:05

Q Okay. 10:31:10

A -- in one or both eyes. 10:31:10

Q So do you have a rough estimate or sense in 2018 approximately how many intravitreal injections of an anti-VEGF that you gave? 10:31:13 10:31:14 10:31:17 10:31:24

MS. KAYALI: Objection. Calls for speculation. Foundation. 10:31:24 10:31:25

You can answer. 10:31:25

THE WITNESS: I would speculate 25 percent of the 3,000. 10:31:28 10:31:28

BY MS. CHACON: 10:31:33

Q All right. So let's fast-forward in time a little bit. We were talking about 2018. Some years go by, and then EYLEA HD, the 8-mg version, is approved in 2023; is that correct? 10:31:33 10:31:51 10:31:54 10:32:00

A I don't know the year it was approved. I could look it up. 10:32:05 10:32:06

Q Okay. I'll -- I'll represent to you 10:32:07

that it was in 2023. 10:32:09

A Thank you. 10:32:12

Q August 18th, 2023, to be exact, but I want to get a sense of your use of EYLEA HD, Doctor. 10:32:13 10:32:16 10:32:21

So when did you first start using EYLEA HD with your patients? 10:32:21 10:32:25

A Because of various administrative and extensive bureaucratic issues of our division being within Johns Hopkins University, it typically takes anywhere from six months to a year for us to get a new medication into our formulary unless there are no other alternatives. 10:32:33 10:32:35 10:32:40 10:32:45 10:32:49 10:32:57

And in this case we already had several alternative anti-VEGF agents, and so this would be an example where it may have taken 6 to 12 months until it was on our formulary to be available to use. 10:33:01 10:33:05 10:33:10 10:33:15 10:33:22

Q So is it fair then to say that you likely were not able to use EYLEA HD in your practice until sometime in 2024? 10:33:23 10:33:24 10:33:25

A I wouldn't want to say a date, but I 10:33:28

would estimate it was six months to a year, approximately -- 10:33:30 10:33:36

Q Uh-huh. 10:33:38

A -- that it would be available for me to use. 10:33:38 10:33:41

Q When EYLEA HD became available to you to use, did you start using it? 10:33:47 10:33:49

A I used it rarely in cases where they already were getting aflibercept 2 mg and had an inadequate response with respect to their visual acuity and still having persistent evidence of VEGF activity despite monthly treatments. 10:33:56 10:34:00 10:34:10 10:34:13 10:34:22

And in that instance, I had the opportunity to switch either to faricimab, Vabysmo, or aflibercept high dose. 10:34:25 10:34:26 10:34:29

And so I would endeavor, if the patient's insurance would cover it, to switch to one or the other. 10:34:37 10:34:39 10:34:42

Q Okay. So you mentioned in one circumstance where a patient was previously getting a 2-mg dose of EYLEA and had an inadequate response with respect to visual acuity and having 10:34:54 10:34:55 10:34:57 10:35:00

persistent evidence of VEGF activity despite monthly treatment. 10:35:04 10:35:06

In that circumstance, you would then switch them to EYLEA HD? 10:35:07 10:35:09

MS. KAYALI: Objection. Foundation. 10:35:12

You can answer. 10:35:15

THE WITNESS: That's a scenario in which I might switch them, and it depends on other factors as well. For example, their insurance might not cover it. 10:35:17 10:35:18 10:35:21 10:35:24

BY MS. CHACON: 10:35:26

Q So -- well, why were you switching -- or could switch a patient to EYLEA HD to address visual acuity and persistent evidence of VEGF activity? 10:35:26 10:35:30 10:35:36 10:35:42

MS. KAYALI: Objection. Vague. Foundation. 10:35:42 10:35:43

You can answer. 10:35:43

THE WITNESS: It was shown in clinical trials that the aflibercept 8 mg gave visual results that were not use than aflibercept 2 mg. 10:35:45 10:35:46 10:35:56

Because of that and because it's 10:36:02

different, it is not aflibercept 2 mg, it seemed reasonable to -- as a therapeutic trial in an individual use such an agent to see if they might respond differently. 10:36:05 10:36:11 10:36:22 10:36:25

BY MS. CHACON: 10:36:32

Q You mentioned that 8 mgs of aflibercept or EYLEA HD is different than the 2-mg dose of EYLEA. 10:36:32 10:36:34 10:36:37

In what ways are they different? 10:36:38

A It's 8 mgs instead of 2 mgs. It's given in .07 mLs instead of .05 mLs. 10:36:42 10:36:47

It has less of a safety track record than 2 mgs because it's been around, I'm presuming since 2018, commercially available. 10:36:54 10:36:59 10:37:06

Q So just trying to understand similarities and differences. So for EYLEA HD and EYLEA, they both utilize aflibercept; is that right? 10:37:12 10:37:13 10:37:17 10:37:21

MS. KAYALI: Objection. Vague. 10:37:22

You can answer. 10:37:24

THE WITNESS: They have aflibercept 2 mg or aflibercept 8 mg. 10:37:29 10:37:32

BY MS. CHACON: 10:37:36

Q Okay. So there's a difference in the 10:37:36

dose. We can agree on that. Is there a 10:37:38

difference in the active ingredient that's being 10:37:41

used? 10:37:43

MS. KAYALI: Objection. Vague. 10:37:43

You may answer. 10:37:47

THE WITNESS: I'm not aware of the 10:37:48

active ingredients that are used in 2 mg 10:37:51

versus 8 mg. 10:37:53

I'm aware that the volume to deliver 10:37:55

it is also different, 70 milliliters instead 10:37:58

of 50 milliliters. 10:38:02

BY MS. CHACON: 10:38:03

Q So just to -- I think we're maybe 10:38:03

misunderstanding each other. So when I say 10:38:10

"active ingredient," I mean, for example, 10:38:12

aflibercept versus an inactive ingredient, which 10:38:15

is all the excipients and other things that go 10:38:18

into making the solution. 10:38:20

Do you understand what I mean by that? 10:38:21

A I understand what you mean by that. 10:38:23

Q Okay. And so you had just said that you are not aware of active ingredients that are used in 2 mgs versus 8 mgs of EYLEA. 10:38:25 10:38:30 10:38:33

Did I understand you correctly? 10:38:37

A At the time that it became available. 10:38:39

(Simultaneous speakers.) 10:38:41

BY MS. CHACON: 10:38:41

Q Sorry. At the time it became available, you were not aware that 8 mgs of EYLEA HD used aflibercept and 2 mgs of EYLEA also used aflibercept? 10:38:42 10:38:45 10:38:49 10:38:53

MS. KAYALI: Objection. Foundation. 10:38:56

You can answer. 10:38:57

THE WITNESS: I was aware -- 10:38:59

BY MS. CHACON: 10:39:00

Q Okay. 10:39:00

A -- that there was 8 mg of aflibercept in the 8 mg, and that there was 2 mg of aflibercept that I'd be injecting in the aflibercept 2 mg. 10:39:01 10:39:05 10:39:06

Q Got it. And I'm not trying to be tricky here, Doctor. I just want to make sure that we agree that both EYLEA HD and EYLEA used 10:39:12 10:39:14 10:39:17

aflibercept; is that correct? 10:39:20

MS. KAYALI: Objection. Asked and 10:39:22

answered. 10:39:23

You can answer. 10:39:23

THE WITNESS: They both use aflibercept. 10:39:25

BY MS. CHACON: 10:39:27

Q Now, as far as comparing EYLEA and EYLEA 10:39:27

HD, you had mentioned some reasons for perhaps 10:39:41

using it is that it was a different dose. 10:39:44

Why would a different dose cause you to 10:39:48

use EYLEA HD over EYLEA? 10:39:50

MS. KAYALI: Objection. Foundation. 10:39:53

Vague. 10:39:56

You can answer. 10:39:58

THE WITNESS: I didn't say it was 10:40:02

because it was a different dose. I said, because 10:40:02

there were clinical trials using 8 mg, the visual 10:40:05

acuity outcomes compared with the aflibercept 2 mg 10:40:08

were not worse. 10:40:14

BY MS. CHACON: 10:40:16

Q So if you were seeing that a patient 10:40:16

wasn't responding in the way that you would have 10:40:21

wanted to 2 mgs of EYLEA, why would you be trying a different drug that demonstrated not worse efficacy? 10:40:24 10:40:29 10:40:35

MS. KAYALI: Objection. Incomplete hypothetical. Foundation. Vague. 10:40:37 10:40:38

THE WITNESS: Because they are different. One is 2 mgs of aflibercept, one is 8 mgs of aflibercept. And perhaps an individual for whatever reason that will respond differently in that particular case that had an inadequate response to 2 mgs. 10:40:46 10:40:47 10:40:50 10:40:57 10:41:02 10:41:05

BY MS. CHACON: 10:41:07

Q I think you mentioned earlier that one of the other reasons that you might use EYLEA HD versus EYLEA -- again, correct me if I'm wrong. 10:41:07 10:41:21 10:41:28 10:41:33

I think you had mentioned something about there being less of a safety track record. Can you explain what you meant by that? 10:41:36 10:41:36 10:41:36

MS. KAYALI: Objection. Foundation. Vague. 10:41:38 10:41:41

You can answer. 10:41:42

1	THE WITNESS: EYLEA 2 mg had been	10:41:46
2	available I believe since 2010. And so we had	10:41:49
3	millions of injections of it being given around	10:41:59
4	the world, and we had the totality of whatever	10:42:01
5	safety reports are provided on that. Not only	10:42:08
6	immediately, but a year later, five years later,	10:42:14
7	and in 2018, eight years later.	10:42:18
8	When EYLEA HD becomes available -- and,	10:42:21
9	again, I'm not including the clinical trial	10:42:27
10	portion of these, but when they become a	10:42:29
11	commercially available -- since the commercial	10:42:31
12	availability of EYLEA HD, we at that time had only	10:42:35
13	a few weeks or months and eventually a year or two	10:42:40
14	or three of safety information, not only in terms	10:42:44
15	of over several years, but in terms of the volume	10:42:49
16	of injections that were given and having that	10:42:54
17	amount of information of millions of injections	10:43:00
18	allows you to identify even rarer adverse events	10:43:05
19	that might not be detected otherwise in the	10:43:10
20	clinical trials and the safety information that	10:43:15
21	those give us at the time of acceptance of the	10:43:17
22	drug or commercial use.	10:43:20

BY MS. CHACON: 10:43:21

Q Okay. So EYLEA HD has been -- or I'm 10:43:37

sorry. EYLEA 2 mg has been out in the world for 10:43:40

over 10 years at that point? Millions of 10:43:46

injections, you said, more information on safety 10:43:50

for EYLEA HD, and -- or I'm sorry. EYLEA 2 mg. 10:43:53

And a reason you might try to switch to 10:43:58

EYLEA HD is because there's less of a safety track 10:44:00

record for EYLEA HD? Am I understanding you 10:44:04

correctly? 10:44:07

MS. KAYALI: Objection. 10:44:08

Mischaracterizes testimony. Foundation. 10:44:09

You can answer. 10:44:12

THE WITNESS: Can you repeat that 10:44:13

question, because I thought there was an error in 10:44:14

it. 10:44:16

BY MS. CHACON: 10:44:16

Q Sure. So I'm just trying to 10:44:16

understand -- kind of sum up and understand what 10:44:18

you were saying so I get it right. You had 10:44:22

mentioned that there was a track record for 10:44:26

EYLEA 2 mgs; right? 10:44:27

MS. KAYALI: Objection. 10:44:31

BY MS. CHACON: 10:44:32

Q Safety track record? 10:44:32

MS. KAYALI: Sorry, Counsel. Objection. 10:44:33

Vague. 10:44:35

You can answer. Excuse me. 10:44:35

Objection. Lacks foundation. 10:44:37

You can answer. 10:44:38

THE WITNESS: The track record in 2018 10:44:41

of, let's say, eight years of safety information 10:44:44

and high volume of injections was greater than the 10:44:47

number of years of safety information on EYLEA HD 10:44:52

and the number of injections that have been done. 10:44:56

BY MS. CHACON: 10:44:58

Q Okay. So that -- is that a reason why 10:44:58

you would not switch to EYLEA HD or why you would 10:45:01

switch to EYLEA HD? 10:45:05

MS. KAYALI: Objection. Foundation. 10:45:07

Vague. 10:45:12

You can answer. 10:45:12

THE WITNESS: It's a reason why I would 10:45:17

not start with EYLEA HD compared with EYLEA 2 mg 10:45:18

because the existing safety information had not yet identified such problems, I would explain that to the patient and indicate that, to the best of the information we have, which is far less safety information that, because you are walking around with impaired vision, we would hope that we might be able to get a better response if we now try an agent that has been shown to be no worse for visual acuity outcomes than the agent that we were using. 10:45:24 10:45:28 10:45:32 10:45:36 10:45:41 10:45:44 10:45:47 10:45:52 10:45:55 10:46:02

BY MS. CHACON: 10:46:03

Q Let's fast-forward to your current practice. What percentage of your current patients that you see would you say are on EYLEA HD? 10:46:03 10:46:11 10:46:15 10:46:19

MS. KAYALI: Objection. Calls for speculation. Foundation. 10:46:22 10:46:23

You can answer. 10:46:25

THE WITNESS: I would estimate, without going to my billing records to get the exact number, that less than 5 percent of the anti-VEGF injections I'm doing are with EYLEA HD but not 10:46:32 10:46:39 10:46:41 10:46:54

zero. 10:47:01

BY MS. CHACON: 10:47:03

Q So for the 5 percent of patients that 10:47:03

you currently treat who would be using EYLEA HD, 10:47:19

what would be the reasons why you would give that 10:47:24

patient EYLEA HD in your current practice? 10:47:28

MS. KAYALI: Objection. Vague. 10:47:31

Foundation. 10:47:34

THE WITNESS: In a patient who did not 10:47:41

have an adequate response to 2 mgs aflibercept in 10:47:43

my current practice, I would discuss with them the 10:47:49

risks and benefits of switching to either 10:47:53

faricimab, Vabysmo or aflibercept high dose 8 mg. 10:48:00

BY MS. CHACON: 10:48:06

Q So what benefits would you counsel the 10:48:06

patient there are for switching to EYLEA HD? 10:48:15

MS. KAYALI: Objection. Incomplete 10:48:20

hypothetical. Foundation. 10:48:24

You can answer. 10:48:25

THE WITNESS: I would hypothesize for 10:48:30

the patient that because the high-dose 8 mg 10:48:32

aflibercept was shown to be not worse than the 10:48:33

visual acuity outcomes using 2 mg that we would hope that it might respond differently in their individual case and perhaps result in some resolution of their VEGF activity that otherwise was not occurring with the aflibercept 2 mg. 10:48:44 10:48:48 10:48:51 10:49:00 10:49:09

BY MS. CHACON: 10:49:13

Q Dr. Bressler, can you further explain to me why you would have this hope that EYLEA HD would generate a different visual outcome for the patient when it was shown in clinical trials to be non-inferior to EYLEA 2 mg? 10:49:13 10:49:20 10:49:24 10:49:26 10:49:29

MS. KAYALI: Objection. Incomplete hypothetical. Lacks foundation. Vague. 10:49:40 10:49:42

You can answer. 10:49:44

THE WITNESS: When a well-designed clinical trial shows that one agent is not worse than the other agent, that means it's likely that it's either the same or superior. And so there's a possibility that, in that individual patient, it will be superior. 10:49:48 10:49:50 10:49:52 10:49:57 10:50:04 10:50:08

BY MS. CHACON: 10:50:10

Q Are you aware of any studies that have 10:50:10

been conducted that demonstrate that EYLEA HD is superior to EYLEA? 10:50:18 10:50:23

MS. KAYALI: Objection. Vague. 10:50:25

You can answer. 10:50:25

THE WITNESS: There are no studies I'm aware where aflibercept high-dose gives superior visual acuity outcomes to aflibercept 2 mg. 10:50:32 10:50:35 10:50:39

I am aware of trials where aflibercept 8 mg gave non-inferior results to 2 mg. And non-inferior includes the possibility that it's the same or superior but not worse. 10:50:41 10:50:45 10:50:46 10:50:50

BY MS. CHACON: 10:50:54

Q Is that based on -- what is that based on? When you say that non-inferior means that it could be the same or superior, what is that based on? 10:50:54 10:51:01 10:51:05 10:51:07

MS. KAYALI: Objection. Vague. 10:51:08

THE WITNESS: That's the definition of what you get from the design of a non-inferiority trial. 10:51:17 10:51:17 10:51:17

If you prove non-inferiority, that means you've proven that it's either the same or 10:51:19 10:51:22

superior but not worse. 10:51:26
BY MS. CHACON: 10:51:27
Q Do you think Regeneron could market the 10:51:27
product as being the same or superior -- could 10:51:32
market EYLEA HD as being the same or superior as 10:51:35
EYLEA? 10:51:35
MS. KAYALI: Objection. Calls for a 10:51:37
legal conclusion. Lacks foundation. And outside 10:51:38
the scope. 10:51:40
THE WITNESS: I'm not a regulatory 10:51:44
agency like the FDA to determine what they could 10:51:45
mark it based on the results of their trials. 10:51:48
BY MS. CHACON: 10:51:51
Q Are you aware of Regeneron making any 10:51:51
claims that EYLEA HD is superior to EYLEA in 10:51:56
visual acuity? 10:51:56
MS. KAYALI: Objection. Outside the 10:51:56
scope of Dr. Bressler's direct testimony. 10:51:58
THE WITNESS: I would clarify by saying 10:52:08
I'm not aware of any prespecified primary outcomes 10:52:10
that show in any retinal disease that 10:52:13
aflibercept 8 mg gives superior visual acuity 10:52:16

outcomes to aflibercept 2 mg. 10:52:21

BY MS. CHACON: 10:52:27

Q Is EYLEA HD more expensive for your patients than EYLEA? 10:52:28 10:52:32

A For the patient's insurance company. I don't know what their internal utilizations of payments are, but I anticipate that it is more expensive than EYLEA 2 mg at this time. 10:52:44 10:52:49 10:52:53 10:52:57

Q So help me understand, to the extent you can, why those insurance companies or patients would pay more for EYLEA HD over EYLEA if there is no clinical trial demonstrating that EYLEA HD is superior to EYLEA? 10:53:04 10:53:07 10:53:13 10:53:18 10:53:23

MS. KAYALI: Objection. Lacks foundation. Incomplete hypothetical. And outside the scope of Dr. Bressler's direct testimony. 10:53:28 10:53:29 10:53:32

THE WITNESS: I could speculate that, because it is approved, which includes, for visual acuity outcomes, that it's non-inferior to EYLEA 2 mg, that someone may choose to use EYLEA 8 mg because the results showed that it was non-inferior, which includes that the outcome 10:53:40 10:53:45 10:53:54 10:54:01 10:54:08 10:54:10

might be the same or it might be superior but not worse. 10:54:16 10:54:18

BY MS. CHACON: 10:54:19

Q Okay. Dr. Bressler, are there any other benefits to EYLEA HD that we haven't discussed yet, in your view? 10:54:19 10:54:24 10:54:28

MS. KAYALI: Objection. Vague. 10:54:29

THE WITNESS: Not that I can think of, but if you can give me an instance, I'm happy to respond to it. 10:54:48 10:54:49 10:54:52

BY MS. CHACON: 10:54:52

Q If we could turn to your declaration, Doctor, and I'd like you to turn to paragraph 141, please. 10:54:52 10:55:18 10:55:22

A And what page is that on, please. 10:55:28

Q Page 71 of your declaration. 10:55:34

A Thank you. 10:55:36

Q And while you're looking, I'm just going to orient us to the fact that where I'm pointing you to is in Section 8 of your declaration entitled "EYLEA HD, Aflibercept 8 Milligrams." 10:56:18 10:56:20 10:56:22 10:56:25

A Okay. Thank you. I'm there. 10:57:03

Q All right. So in this section, Doctor, including in paragraph 141, you discuss some of the information regarding EYLEA HD; is that correct? 10:57:04 10:57:06 10:57:14 10:57:16

A That is correct. 10:57:18

Q And in paragraph 141, you have summarized to some degree that there were three global phase three clinical trials: Pulsar, photon, and quasar supporting EYLEA HD; is that correct? 10:57:19 10:57:24 10:57:28 10:57:31 10:57:35

A That is correct. 10:57:37

Q And in the last sentence there, you say, "In all studies, extended dosing using EYLEA HD achieved clinical non-inferiority endpoints compared with the standard dose of EYLEA 2 mg while demonstrating a comparable safety profile between the two drugs." Correct? 10:57:38 10:57:41 10:57:45 10:57:50 10:57:51 10:57:55

A That is correct. 10:57:58

Q Now, you don't mention anything here in the discussion of clinical trials about superiority; right? 10:57:58 10:58:02 10:58:04

A That is correct. 10:58:06

Q And next paragraph, 142, you talk about some of the benefits that EYLEA HD offers over other anti-VEGF agents when used on a fixed dosing schedule according to its label; is that right? 10:58:06 10:58:10 10:58:14 10:58:20

A That is correct, according to its label. 10:58:22

Q Okay. And what are the benefits that you've identified in this paragraph for EYLEA HD as compared to other anti-VEGF agents? 10:58:26 10:58:29 10:58:31

A Going on to the second sentence, "According to its FDA-approved label, the fixed dosing schedule for EYLEA HD is every 8 to 16 weeks after an initial loading period -- after the loading period, which reduces the average number of required injections when compared with the fixed dosing schedules specified in the labels for ranibizumab or aflibercept 2 mg." 10:58:35 10:58:36 10:58:42 10:58:46 10:58:47 10:58:50 10:58:53 10:58:58

Q So it's your opinion that a benefit of EYLEA HD is that it reduces the average number of required injections when compared to the fixed dosing schedule specified in the labels for either ranibizumab or EYLEA 2 mg; is that right? 10:59:03 10:59:06 10:59:09 10:59:15 10:59:16

A Yes. And I would emphasize specialized 10:59:21

in the labels. 10:59:24

Q Why do you emphasize that? 10:59:26

MS. KAYALI: Objection. Vague. 10:59:31

THE WITNESS: There's no evidence that 10:59:35

giving EYLEA 2 mg at the regimen at which EYLEA 10:59:37

high dose was given would be any different. 10:59:48

MS. CHACON: I'm going to introduce an 11:00:18

exhibit that's already been marked in this 11:00:19

proceeding as Alvotech Exhibit 1054. It is a copy 11:00:21

of the 2024 label for EYLEA HD. 11:00:25

(Petitioner's Exhibit 1054 was marked 11:00:43

for identification, the original of which is 11:00:43

attached hereto.) 11:00:43

MS. KAYALI: Thank you. 11:00:45

THE WITNESS: Thank you. 11:00:45

BY MS. CHACON: 11:00:46

Q So, Doctor, you've just been handed a 11:00:46

copy of Exhibit 1054 which, as I mentioned, is a 11:00:49

copy of the 2024 version of the EYLEA HD label. 11:00:52

Feel free to go ahead and take a moment 11:00:57

to look through that, but I am going to ask you -- 11:00:59

start with asking you some questions regarding 11:01:03

the -- the dose when you're ready. 11:01:05

A Thank you. I'm ready. 11:01:34

Q Okay. Are you familiar with the EYLEA HD label, Doctor? 11:01:35 11:01:36

MS. KAYALI: Objection. Vague. 11:01:43

You can answer. 11:01:44

THE WITNESS: I don't know what you mean by "familiar." I have looked at the label previously. 11:01:45 11:01:46 11:01:49

BY MS. CHACON: 11:01:50

Q Okay. Have you ever looked at the label in your practice prior to your involvement in this matter? 11:01:50 11:01:53 11:01:56

A I looked at the label previously in my practice and in my job both to look at the -- some of the clinical trial results, for example, on page 16 of 20 in Figure 8, to see if I was generally aware of the information in here compared with what I knew from the clinical trials that I read. 11:02:02 11:02:04 11:02:07 11:02:14 11:02:23 11:02:29 11:02:33

I also have looked at the label to look at the instructions for drawing up the medication 11:02:33 11:02:37

starting on page 3 of 20, Section 2.5 called "Preparation for Administration" so that, when I was first using it, I was indeed preparing it and administering -- administering it properly. 11:02:45 11:02:45 11:02:49 11:02:55

Q Okay. Let's look at page 2. And it's under the heading 2, "Dosage in an administration." 11:03:07 11:03:14 11:03:19

And under the -- Section 2.1, "Important Injection Instructions," it instructs that a 30 gauge half-inch sterile injection needle is needed. 11:03:21 11:03:28 11:03:31 11:03:34

Do you see that? 11:03:35

A I see that. 11:03:36

Q Okay. And when you've used EYLEA HD in your practice, is that the needle gauge that you utilize? 11:03:37 11:03:40 11:03:46

A That is the needle gauge that I utilize. 11:03:46

Q Now, below that, in Sections 2.2 and 2.3 and 2.4 -- actually, let me go back and ask you a different question before we move on. 11:03:51 11:03:56 11:04:01

Is the 30-gauge needle the same needle gauge that you'd use for administration of EYLEA 2 11:04:03 11:04:08

mgs? 11:04:09

A It is. 11:04:10

Q Okay. Now let's fast-forward to Sections 2.2, 2.3, and 2.4. And these indicate the dosage and administration instructions for neovascular wet age-related macular degeneration, diabetic macular edema, and diabetic macular retinopathy; is that right? 11:04:12 11:04:15 11:04:22 11:04:28 11:04:28 11:04:33

A That is correct. 11:04:36

Q Okay. And for each of these, it appears that EYLEA HD is administered every four weeks for the first three doses. 11:04:37 11:04:42 11:04:50

And then administration after that is extended to every 8 to 16 weeks for nAMD and DME and then every 8 to 12 weeks for diabetic retinopathy. 11:04:54 11:04:56 11:05:05 11:05:09

Do you see that? 11:05:13

MS. KAYALI: Objection. Compound. Vague. 11:05:14 11:05:15

You can answer if you can. 11:05:15

THE WITNESS: I was disagreeing with your term "administered." This is the recommended 11:05:18 11:05:19

dose that's in the label.
BY MS. CHACON:
Q Okay. You would agree, though, that it's the recommended dose that's in the label for each of these conditions is what's set forth in these sections; is that right?
A Yes.
Q Okay. In your practice -- and let's just start with wet AMD as an example. Are there any patients that you've administered EYLEA HD that have wet AMD?
A There are.
Q And in those circumstances, did you adhere to the recommended dosing schedule?
MS. KAYALI: Objection. Compound. Vague.
You can answer.
THE WITNESS: No, because this starts with the recommended dose for the first three doses.
And, as I said previously, when I have an individual with me with vascular AMD, I almost

always would start with 2 mg aflibercept. 11:06:42

BY MS. CHACON: 11:06:47

Q Okay. And are there any circumstances where you've switched those 2 mg of aflibercept patients to 8 mgs aflibercept? 11:06:47 11:06:50 11:06:52

A Yes, there are. 11:06:58

Q And after those patients have been switched, did you adhere to the dosing recommendations in Section 2.2 that's set forth in the EYLEA HD label? 11:07:00 11:07:02 11:07:07 11:07:14

MS. KAYALI: Objection. Vague. Compound. 11:07:15 11:07:16

You may answer. 11:07:17

THE WITNESS: Not necessarily, because these are the recommendations when you're initiating a patient with aflibercept 8 mg. 11:07:18 11:07:19 11:07:21

And I'm talking about a situation where I'm switching someone from aflibercept 2 mg to aflibercept 8 mg. 11:07:27 11:07:30 11:07:33

So there may be numerous scenarios as I'm treating them. I might be doing it monthly for three doses or four doses or six doses. 11:07:35 11:07:41 11:07:44

I might be doing it monthly for one dose and then see a remarkable response and decide, because that patient had been treated for the last four years the aflibercept 2 mgs and never getting better, that perhaps I could give them one more dose. 11:07:49 11:07:52 11:07:56 11:07:59 11:08:02 11:08:06

They come back yet another month later, and I say, I don't think adding a third dose is worth the risks of the benefits. 11:08:06 11:08:06 11:08:11

And this recommendation is about initiating people with EYLEA that have not been treated for neovascular AMD previously. 11:08:14 11:08:15 11:08:19

BY MS. CHACON: 11:08:22

Q Do you have any patients, Dr. Bressler, who start on EYLEA HD? 11:08:23 11:08:25

MS. KAYALI: Objection. Vague. 11:08:32

You can answer. 11:08:36

THE WITNESS: Not that I can recall. I can again hypothesize. If there was a patient who was treated with EYLEA 2 mg, had an inadequate response for years, would switch to EYLEA HD, and had an excellent response and it remained 11:08:37 11:08:38 11:08:46 11:08:51 11:08:58

excellent. 11:08:59

And then they come to me with their other eye for the first time developing neovascular AMD, I might find it reasonable to start that person on EYLEA HD, but I have not had such a person yet. 11:09:00 11:09:03 11:09:03 11:09:06 11:09:13

BY MS. CHACON: 11:09:14

Q So you had mentioned, Doctor, you previously had seen the label prior to this proceeding, that you might have looked at some of the clinical trial or clinical study information in the label. 11:09:14 11:09:28 11:09:31 11:09:34 11:09:37

Did I understand you correctly? 11:09:37

A That's correct. 11:09:39

Q Okay. And that begins on page 15 of Exhibit 1054. So if you could turn there for me, please. 11:09:39 11:09:43 11:09:53

All right. And we're just going to look for a moment at Section 14.1, which summarizes some of the data from the pulsar study. 11:09:59 11:10:01 11:10:05

Can you see where I'm at? 11:10:09

A I do. I just want to read it for a 11:10:12

minute to remind myself. 11:10:14

Okay. Thank you. 11:11:57

Q Sure. I want to draw your attention to Table 2 for a moment. 11:11:59 11:12:03

What does Table 2 set forth? 11:12:06

A Table 2 is looking at the efficacy outcomes of the full analysis set in the pulsar study. 11:12:13 11:12:19 11:12:19

Q Okay. And it reports on the mean change in BCVA as measured by ATDRS letter score from baseline at week 48; correct? 11:12:25 11:12:29 11:12:33

A Correct. 11:12:36

Q And for the EYLEA HD 12-week and 16-week populations, they exhibited a lesser mean change and BCVA as compared to EYLEA 2 mg administered at 8 weeks; is that correct? 11:12:36 11:12:44 11:12:49 11:12:57

MS. KAYALI: Objection. Vague. 11:13:00

You can answer. 11:13:01

THE WITNESS: Could you repeat the question, please. Sorry. 11:13:02 11:13:03

BY MS. CHACON: 11:13:04

Q For the EYLEA HD 12-week and 16-week 11:13:04

populations, they exhibited a lesser mean change in BCVA as compared to EYLEA 2 mgs administered at eight weeks? 11:13:11 11:13:14 11:13:20

MS. KAYALI: Objection. Vague. 11:13:22

You can answer. 11:13:25

THE WITNESS: The numbers are numerically less. Yes. 11:13:27 11:13:28

BY MS. CHACON: 11:13:31

Q Why do you say "numerically less"? 11:13:31

A This is the sample of 335, 338, and 336 people, and so there's going to be biologic variability in the people that are enrolled in each of those groups. 11:13:37 11:13:42 11:13:47 11:13:49

And so, when you said that they are -- I forget the wording. You'd have to repeat the question again, but I'm recalling different. 11:13:51 11:13:53 11:13:55

You'd have to do a pairwise comparison to look at the differences and then look at the confidence symbol around that to see if they are likely or statistically different. 11:13:59 11:14:02 11:14:04 11:14:10

Now, that wasn't done for that first row that you said. That was done for the least square 11:14:12 11:14:15

mean change from baseline. 11:14:16

Q Okay. And what does the least square 11:14:20

mean change from baseline tell you? 11:14:21

MS. KAYALI: Objection. Vague. 11:14:25

You can answer. 11:14:30

THE WITNESS: If you mean what is the 11:14:31

least squared mean change compared with the mean 11:14:32

change, it's looking for an adjustment in the 11:14:35

baseline visual acuity, which is a way of trying 11:14:40

to adjust for the fact that some participants may 11:14:46

walk in with visual acuity of 2050 equivalent. 11:14:52

Some may walk in with 2200 equivalent. 11:14:57

And those might affect the ability to 11:15:00

have an improvement in vision. So this tries to 11:15:02

adjust for that, and so that's what the -- the 11:15:05

square mean change from baseline tells me for 11:15:08

those outcomes. 11:15:12

BY MS. CHACON: 11:15:13

Q And specifically for the data that we 11:15:13

see here in Table 2 for least squared mean change 11:15:15

from baseline, what does that tell you about how 11:15:16

the EYLEA HD performed in comparison to EYLEA? 11:15:21

MS. KAYALI: Objection. Foundation. Vague. 11:15:27 11:15:30

You can answer. 11:15:31

THE WITNESS: In the non-inferiority design, the differences are looked at in the least square mean as that was, I believe, the primary outcome. 11:15:33 11:15:36 11:15:37 11:15:40

And it shows you that the point estimate is minus 1.0 for EYLEA HD Q12. It's minus 1.1 letter for the EYLEA HD Q16. 11:15:41 11:15:44 11:15:50

And the 95 percent confidence around those crosses zero, showing us that we do not see a difference between those numerical values of 6.1, 5.9, and 7.0 on a statistically analyzed basis. 11:15:54 11:15:56 11:16:02 11:16:07 11:16:18

BY MS. CHACON: 11:16:18

Q Okay. In the -- I'm going to point you to now, Doctor, to the paragraph -- two paragraphs above Table 2 starting with both HD Q12 and HD Q16 treatments. 11:16:18 11:16:24 11:16:28 11:16:32

Do you see where I'm pointing you to? 11:16:33

MS. KAYALI: Actually, Counsel, I have 11:16:35

to ask you to repeat that. I couldn't hear. 11:16:37
BY MS. CHACON: 11:16:38
Q So Table 2. Two paragraphs above, so 11:16:38
first paragraph is "efficacy results," next 11:16:43
paragraph is both HD Q12 and HD Q16 treatments. 11:16:46
Do you see where I'm pointing you to, 11:16:50
Doctor? 11:16:52
A I do see that paragraph, yes. 11:16:52
Q Okay. 11:16:54
A Thank you. 11:16:55
Q Now, the second sentence there says, "In 11:16:56
patients completing week 48, the mean number of 11:17:00
injections administered were 5.2 in the HD Q16 11:17:03
group, N equals 312. 6.1 in the HD Q12 group, N 11:17:07
equals 316. And 6.9 in the EYLEA Q8 group, N 11:17:18
equals 309." 11:17:22
Do you see that? 11:17:22
A I do see that. 11:17:23
Q So this is reporting here that the EYLEA 11:17:25
HD groups had a lower mean number or fewer mean 11:17:30
number of injections administered as compared to 11:17:36
the EYLEA group; is that right? 11:17:39

MS. KAYALI: Objection. Vague. 11:17:41
You can answer. 11:17:43
THE WITNESS: Those numbers are 11:17:48
numerically different, and they're lower in the HD 11:17:49
groups. 11:17:53
BY MS. CHACON: 11:17:54
Q So for the HD Q16 group, it's 1.7 11:17:54
injections lower; is that correct? 11:18:02
MS. KAYALI: Objection. Vague. 11:18:08
THE WITNESS: The point estimate 11:18:15
differences are 1.7 difference in the 6.9 versus 11:18:16
the 5.2. That does equal 1.7. 11:18:19
BY MS. CHACON: 11:18:22
Q And for the HD Q12 group as compared to 11:18:22
the EYLEA Q8 group, it's a .8 injection 11:18:26
difference; is that correct? 11:18:28
A The point estimate difference is a .8 11:18:32
difference. 11:18:37
Q Now, you opined in paragraph 142 that 11:18:39
EYLEA HD offers benefits over other anti-VEGF 11:18:43
agents, including EYLEA, given that the -- reduce 11:18:45
the average number of required injections; 11:18:51

correct? 11:18:55

A I said, according to its FDA-approved 11:18:56

label, the fixed dosing for EYLEA HD is every 8 11:18:59

to 16 weeks after the loading period which reduces 11:19:03

the average number of required injections when 11:19:06

compared with the fixed dosing schedules specified 11:19:09

in the labels. 11:19:12

Q Correct. And I'm asking you why you 11:19:15

believe that to be a clinical benefit of EYLEA 11:19:16

HD. 11:19:20

MS. KAYALI: Objection. Vague. 11:19:22

THE WITNESS: I don't recall saying that 11:19:24

it's a clinical benefit. I indicated that it 11:19:26

offers benefits used on a fixed dosing schedule 11:19:31

according to its label. 11:19:34

BY MS. CHACON: 11:19:36

Q Okay. Why do you believe it's a 11:19:36

benefit? 11:19:39

A It's possible but not proven because the 11:19:49

study was not designed to determine that, that you 11:19:53

could give fewer injections without compromising 11:19:58

the visual acuity. 11:20:03

However, we do not have a treatment arm where the EYLEA 2 mg was also given at a fixed dosing schedule every 8 to 16 weeks after the loading period. So that is a potential benefit without having the data to know if it's a true benefit. 11:20:06 11:20:12 11:20:18 11:20:22 11:20:31 11:20:36

Q So the idea that you could give your injections without compromising the visual acuity -- why do you believe that to be a potential benefit of EYLEA HD? 11:20:37 11:20:41 11:20:43 11:20:47

MS. KAYALI: Objection. Foundation. Vague. 11:20:49 11:20:51

THE WITNESS: It's theoretically possible, but we do not have a trial to determine if -- that you would be able to give fewer injections with the EYLEA HD compared with EYLEA 2 mg. 11:21:00 11:21:02 11:21:07 11:21:10 11:21:14

However, it's also possible that if we had an arm where we allowed the EYLEA 2 mg to be given by the same regimen as the EYLEA HD, that we would show the same number of injections or even fewer injections. 11:21:16 11:21:20 11:21:26 11:21:31 11:21:34

BY MS. CHACON: 11:21:35

Q So, Dr. Bressler, that's not my 11:21:35

question. I understand it's your opinion that it 11:21:37

could be theoretical or not theoretical if we had 11:21:39

another study. 11:21:44

My question is directed to what you said 11:21:45

in your report in paragraph 152, which is that 11:21:48

"EYLEA HD offers benefits over other anti-VEGF 11:21:50

agents when used on a fixed dosing schedule 11:21:54

according to its label," and I'd like to 11:21:59

understand what benefit or why do you believe that 11:22:01

to be true? 11:22:05

MS. KAYALI: Counsel, you're referring 11:22:06

to paragraph 152 of Dr. Bressler's -- 11:22:08

MS. CHACON: 142. Excuse me. 142. 11:22:10

MS. KAYALI: Okay. Well, I object to 11:22:14

the question as vague and argumentative. 11:22:15

You can answer. 11:22:17

THE WITNESS: If you are confined to 11:22:25

treating only according to its label, then you 11:22:26

would have benefits of an average number of 11:22:34

required injections that are reduced compared with 11:22:39

the fixed dosing schedule as specified on the label or aflibercept. 11:22:43 11:22:45

BY MS. CHACON: 11:22:50

Q What benefit does a reduced number of injections have for a patient receiving aflibercept? 11:22:50 11:22:53 11:22:57

MS. KAYALI: Objection. Vague. Foundation. 11:23:03 11:23:03

You can answer. 11:23:04

THE WITNESS: It has benefits of not taking on the risks or expense of additional injections if there's no sacrifice to the visual acuity. 11:23:10 11:23:12 11:23:16 11:23:23

BY MS. CHACON: 11:23:24

Q So every time a patient receives an intravitreal injection of aflibercept, there are potential safety risks associated with that injection. 11:23:24 11:23:29 11:23:38 11:23:40

Would you agree with that? 11:23:41

A I would agree with that. 11:23:42

Q Okay. And so if we reduce the number of injections a patient might have, that would reduce 11:23:43 11:23:47

the risk of some of those safety issues associated with injection of aflibercept. 11:23:52 11:23:56

Would you agree with that? 11:24:01

A Could you just say it one more time? I was listening to the first part and then didn't get to the second part. 11:24:02 11:24:05 11:24:07

Q If we reduce the number of injections a patient might have, that would reduce the risk of some of the safety issues associated with injection of aflibercept. 11:24:08 11:24:10 11:24:13 11:24:16

Would you agree with that? 11:24:18

MS. KAYALI: Objection. Incomplete hypothetical. 11:24:20 11:24:22

You can answer. 11:24:23

THE WITNESS: If there were no sacrifice to the visual acuity. 11:24:24 11:24:26

BY MS. CHACON: 11:24:28

Q Is that a "yes"? 11:24:28

MS. KAYALI: Objection. Mischaracterizes testimony. Asked and answered. 11:24:29 11:24:31

You can answer. 11:24:35

THE WITNESS: So now please just repeat 11:24:39

1	the question.	11:24:40
2	BY MS. CHACON:	11:24:41
3	Q Sure. If we reduce the number of	11:24:41
4	injections a patient might have, that would reduce	11:24:43
5	the risk of some of the safety issues associated	11:24:46
6	with the injection of aflibercept.	11:24:49
7	Would you agree with that?	11:24:52
8	MS. KAYALI: Objection. Incomplete	11:24:53
9	hypothetical. Asked and answered.	11:24:55
10	You can answer.	11:24:56
11	THE WITNESS: I would agree with that if	11:24:59
12	it did not sacrifice any visual acute benefits.	11:25:00
13	MS. KAYALI: And, Counsel, this might be	11:25:07
14	another good time -- I think we're at about	11:25:09
15	90 minutes again, which is turning out to be my	11:25:12
16	limit, for a break.	11:25:14
17	Dr. Bressler, would you like a break?	11:25:16
18	MS. CHACON: I actually have one or two	11:25:18
19	more questions, so if you'll bear with me, Doctor,	11:25:20
20	on this line, and then we can take a break.	11:25:22
21	MS. KAYALI: Okay. I can let it go for	11:25:25
22	another minute, but after that I'll defer to the	11:25:26

witness. 11:25:29

MS. CHACON: Is that okay, Dr. Bressler? 11:25:30

THE WITNESS: I'll do a minute. 11:25:32

BY MS. CHACON: 11:25:33

Q All right. Earlier today we were 11:25:34
talking about some of the injection procedures 11:25:35
that you had utilized for EYLEA in your practice. 11:25:36

Do you recall that? 11:25:39

MS. KAYALI: Counsel, if we're going 11:25:41
into a different topic, we need to take a break. 11:25:42

MS. CHACON: It's not a different topic, 11:25:45
Counsel, we're circling back to EYLEA HD. So let 11:25:46
me finish the question for Dr. Bressler. 11:25:47

BY MS. CHACON: 11:25:50

Q Dr. Bressler, would you like me to 11:25:50
repeat the question? 11:25:52

A Please. 11:25:53

Q Okay. Earlier today we had talked about 11:25:54
some of the injection procedures that you had 11:25:56
utilized for EYLEA in your practice. 11:25:58

Do you recall that? 11:26:00

A I do. 11:26:01

Q And do you recall you telling me that a preinjection procedure was to use a Q-Tip to push on the Stelara to reduce volume? 11:26:01 11:26:02 11:26:06

A Inside of the vitreous; correct. 11:26:10

Q Okay. Do you utilize the same procedure when administering EYLEA HD to your patients? 11:26:15 11:26:18

A I do administer the same procedure. 11:26:23

MS. CHACON: All right, Counsel, we can take a break. 11:26:26 11:26:27

MS. KAYALI: Perfect. 11:26:28

THE VIDEOGRAPHER: We are going off the record. The time is 11:26. 11:26:30 11:26:31

(Recess.) 11:26:34

THE VIDEOGRAPHER: We are going back on the record. The time is 11:45. 11:45:00 11:45:02

BY MS. CHACON: 11:45:04

Q Dr. Bressler, in Section 4 of your declaration, you provide some summary of the '036 patent; is that correct? 11:45:04 11:45:14 11:45:19

A In Section 4, I provide information on the '036 patent. 11:45:45 11:45:51

Q Okay. Now, I know in subsection A, you 11:45:52

provide a reproduction of the challenged claims, but just for purposes and the sake of reference, I'm going to have the court reporter hand you what's been marked in this proceeding already as Alvotech Exhibit 1001, which is a copy of the '036 patent. 11:45:56 11:46:01 11:46:05 11:46:06 11:46:08 11:46:11

(Petitioner's Exhibit 1001 was marked for identification, the original of which is attached hereto.) 11:46:36 11:46:36 11:46:36

THE STENOGRAPHER: Here you go, sir. 11:46:37

THE WITNESS: Thank you. 11:46:39

BY MS. CHACON: 11:46:43

Q So feel free to take a look. This is a copy of the '036 patent, which you summarize in your Section 4. Let me know when you're ready. 11:46:43 11:46:46 11:46:49

A Okay. I'm ready. Thank you for waiting. I'm ready. 11:46:51 11:48:22

Q All right. Is -- Exhibit 1001 is the '036 patent. Did you review the '036 patent in preparation for your deposition, Dr. Bressler? 11:48:24 11:48:33 11:48:37

A I did. 11:48:39

Q Did you review it cover to cover? 11:48:41

A I did not. 11:48:43

Q In preparing your opinions set forth in your declaration, did you review the '036 patent cover to cover? 11:48:45 11:48:48 11:48:52

MS. KAYALI: Objection. Vague. 11:48:53

You can answer. 11:48:54

THE WITNESS: I did not review the '036 patent cover to cover. 11:48:58 11:48:59

BY MS. CHACON: 11:49:01

Q What portions of the '036 patent do you recall reviewing in preparing your opinions in your declaration? 11:49:01 11:49:03 11:49:08

A I recall looking at the patent as it related to the summary that I had on page 16 and 17 in my declaration, and I recall at various times during preparation for this deposition we reviewed certain areas of the patent, but I'm not familiar with it enough to tell you specifically which those were. 11:49:51 11:49:55 11:50:02 11:50:16 11:50:24 11:50:27 11:50:30

Q Dr. Bressler, prior to this matter, had you ever reviewed any patents before? 11:50:34 11:50:37

A I have reviewed a patent that I wrote at 11:50:42

Johns Hopkins University with Applied Physics Lab engineers on using AI to evaluate images of the retina in macular degeneration. 11:50:47 11:50:50 11:50:54

Q Are you an inventor on that patent? 11:50:58

A I am an inventor on that patent. 11:51:01

Q Do you generally -- what is your general understanding in terms of how a patent is structured? 11:51:03 11:51:05 11:51:08

MS. KAYALI: Objection. Vague. Calls for a legal conclusion. 11:51:12 11:51:15

You can answer. 11:51:16

THE WITNESS: My general understanding is that it's quite a complex process outside of my ability to be able to do anything outside of the clinical input that I might give to the content of a patent, if that were so indicated. 11:51:22 11:51:23 11:51:27 11:51:33 11:51:38

BY MS. CHACON: 11:51:45

Q Do you understand that usually at the back of a patent there are claims? 11:51:45 11:51:47

A I recognize that as I have looked at this patent in preparation for this deposition. 11:51:53 11:51:57

Q And before the claims, there's typically 11:52:01

pages and pages of information. 11:52:07

Are you familiar with the term 11:52:10

"specification"? 11:52:11

A I'm not familiar with the term 11:52:14

"specification." 11:52:15

Q So do you understand, Doctor, that a 11:52:24

patent -- what's in the claims, for lack of a 11:52:27

better way to say it, really defines what the 11:52:31

invention is, what's being claimed? 11:52:35

Do you have a general understanding of 11:52:37

that? 11:52:38

A I have a general understanding of that. 11:52:39

Q Okay. Great. So for preparing your 11:52:41

opinions for this case, did you review all of the 11:52:45

claims that start on page 78 of Exhibit 1001? 11:52:49

MS. KAYALI: Objection. Vague. 11:52:59

You can answer. 11:53:00

THE WITNESS: I read through all of 11:53:08

these claims at one point or another. 11:53:09

BY MS. CHACON: 11:53:11

Q Okay. Dr. Bressler, do you recall when 11:53:11

the first time it was that you looked at the '036 11:53:26

patent? 11:53:29

A I don't recall when except it would have been within the time period of initiating evaluation of these exhibits and preparing my opinion in this declaration. 11:53:33 11:53:36 11:53:40 11:53:43

Q Do you recall whether it was before you received your first draft in your declaration? 11:53:45 11:53:47

A I don't recall. It might have been. 11:53:52

Q Okay. So typically patents try to claim something new or novel; right? That's the -- sort of the give and take for a patent office giving you a patent. 11:53:58 11:54:03 11:54:08 11:54:12

Do you have a general understanding of that? 11:54:12 11:54:14

MS. KAYALI: Objection. Calls for a legal conclusion. 11:54:14 11:54:15

THE WITNESS: I have a general understanding with the caveat, I know that patents are quite complex from a legal standard, which I would not be able to explain further. 11:54:22 11:54:23 11:54:25 11:54:30

BY MS. CHACON: 11:54:35

Q Sure. And so the inventors on this '036 11:54:35

patent is Kenneth S. Graham and Saurabh Wadhwa. 11:54:39
Do you see that on the first page? 11:54:47
A I do. 11:54:49
Q Okay. And do you, after having reviewed 11:54:49
the '036 patent, have a sense of what the problem 11:54:53
was that was identified by these inventors that 11:54:58
they were trying to solve? 11:55:02
MS. KAYALI: Objection. Calls for a 11:55:03
legal conclusion. 11:55:05
THE WITNESS: I would not be able to 11:55:12
characterize what the problem was. 11:55:14
BY MS. CHACON: 11:55:15
Q Would you be able to characterize what 11:55:17
it was they invented? 11:55:19
MS. KAYALI: Objection. Calls for a 11:55:23
legal conclusion. 11:55:24
THE WITNESS: What they invented are 11:55:29
listed on page 18 of my declaration starting with 11:55:31
number 1, a method for treating an angiogenic eye 11:55:35
disorder in a human subject in need thereof -- in 11:55:39
need thereof comprising administering 11:55:44
intravenously into the eye of a subject of about 11:55:45

100 mL or less, at least about 8-mg of a VEGF receptor fusion protein and so forth. 11:55:47 11:55:53

BY MS. CHACON: 11:55:57

Q Okay. So for this invention that's discussed, what you just read to me is Claim 1; right, of the '036 patent? 11:55:57 11:56:03 11:56:06

A That is correct. 11:56:09

Q Okay. So what was Claim 1 -- what problem was Claim 1 aimed to solve? 11:56:10 11:56:13

MS. KAYALI: Objection. Foundation. Calls for a legal conclusion. 11:56:15 11:56:16

THE WITNESS: Again, I'm not a legal expert to be able to answer that question. 11:56:23 11:56:24

BY MS. CHACON: 11:56:28

Q I appreciate that, and I'm not asking for a legal opinion. Doctor, I'm asking based on your review of the patent, and you've provided opinions on why these claims are not unpatentable. So I'd like to understand what you understood the problem to be that they were solving. 11:56:28 11:56:30 11:56:32 11:56:35 11:56:44 11:56:46

MS. KAYALI: Objection. Lacks foundation. Calls for a legal conclusion. Asked 11:56:48 11:56:49

and answered.

THE WITNESS: The problem they're solving are as listed in the declaration here.

BY MS. CHACON:

Q So the problem they were solving is the claims?

MS. KAYALI: Objection. Mischaracterizes testimony. Lacks foundation.

You can answer.

THE WITNESS: You'd have to repeat the question.

BY MS. CHACON:

Q I'm just trying to understand your response. So are you saying that the problem they're trying to solve -- and you pointed me to where you just read, which is page 18 in your report, which copies the claims.

Am I understanding you correctly?

MS. KAYALI: Objection. Vague. Lacks foundation and mischaracterizes testimony.

THE WITNESS: I'm indicating what the claims are in the '036 patent.

BY MS. CHACON: 11:57:42

Q If you could go to paragraph 35 in your declaration, and that starts off with a summary sentence that says, "The '036 patent released ophthalmic formulations containing high concentrations of VEGF receptor fusion protein, at least about 8 mg in a volume of about 100 mL or less with a pharmaceutically suitable viscosity in particularly suited for intravitreal administration." 11:57:42 11:58:02 11:58:12 11:58:15 11:58:18 11:58:21 11:58:26 11:58:28 11:58:28

Do you see that paragraph? 11:58:30

A I do see that. 11:58:32

Q Okay. Now, down below that, you include some portions of the specification, which is sort of everything before the claims, and you point to -- there's a sentence that starts with "however." 11:58:34 11:58:37 11:58:40 11:58:43 11:58:47

Do you see that about midway through the paragraph? 11:58:48 11:58:50

A I do. 11:58:56

Q And you include this in paragraph 35, and it says, "However, there's a pressing need for 11:58:56 11:58:58

more effective and durable therapies in clinical practice, as monthly or bimonthly intravitreal injections represent a significant treatment burden on patients, caregivers, and physicians." 11:59:02 11:59:05 11:59:05 11:59:08

Do you see that? 11:59:11

A I do. 11:59:13

Q Okay. What do you understand that portion of the specification to be conveying? 11:59:13 11:59:15

MS. KAYALI: Objection. Vague. 11:59:19

You can answer. 11:59:21

THE WITNESS: That there's a need for anti-VEGF agents that are more effective and more durable in clinical practice than just monthly or bimonthly injections. 11:59:27 11:59:30 11:59:45 11:59:51

BY MS. CHACON: 11:59:54

Q And that's because monthly or bimonthly intravitreal injections represent a significant treatment burden on physicians, caregivers, and physicians; is that right? 11:59:54 11:59:58 12:00:03 12:00:09

A That is true. 12:00:13

Q Do you agree, Dr. Bressler, that, as of May 2018, that there was this need that's been 12:00:16 12:00:20

articulated in the specification that you included in page 35 -- or paragraph 35? 12:00:24 12:00:28

MS. KAYALI: Objection. Vague. 12:00:31

You can answer. 12:00:33

THE WITNESS: In 2018, there was a need for more effective and more durable therapies in clinical practice. 12:00:38 12:00:39 12:00:43

BY MS. CHACON: 12:00:45

Q And was there also a need to reduce significant treatment burden on patients, caregivers, and physicians in 2018? 12:00:45 12:00:51 12:00:53

MS. KAYALI: Objection. Vague. 12:00:56

You can answer. 12:00:57

THE WITNESS: There was a need to reduce the treatment burden on patients and caregivers and physicians. 12:01:00 12:01:02 12:01:07

BY MS. CHACON: 12:01:08

Q And so what is your understanding of how the claimed invention solved this problem, if it did? 12:01:08 12:01:25 12:01:30

MS. KAYALI: Objection. Incomplete -- 12:01:31

excuse me. Objection. Vague. Lacks foundation. 12:01:35

THE WITNESS: I didn't talk about solving a problem. I said at the end of that paragraph that the '036 patent describes high concentration ophthalmic formulations of VEGF receptor fusions proteins, primarily aflibercept, that satisfy this pressing need and methods of using them to treat angiogenic eye disorders. 12:01:41 12:01:42 12:01:45 12:01:50 12:01:50 12:01:51 12:01:57 12:01:59

BY MS. CHACON: 12:02:03

Q I want to go back to that "however" sentence, and there's a discussion there, as we said, about more effective and durable therapies in clinical practice. 12:02:03 12:02:08 12:02:11 12:02:16

And I want to ask you, Dr. Bressler, what do you understand "durable therapies" to mean? 12:02:18 12:02:22 12:02:25

MS. KAYALI: Objection. Vague. 12:02:26

You can answer. 12:02:27

THE WITNESS: More durable therapies, in the setting of using anti-VEGF, mean having the ability to give treatment less frequently without sacrificing visual acuity. 12:02:36 12:02:37 12:02:46 12:02:57

BY MS. CHACON: 12:02:59

Q Is that the only meaning that you would ascribe to the term "durability" in the context of using anti-VEGF treatments as of May 2018? 12:02:59 12:03:14 12:03:20

MS. KAYALI: Objection. Vague. Lacks foundation. 12:03:25 12:03:28

You can answer. 12:03:29

THE WITNESS: I would have to think about other possibilities. One that comes to mind is that it would also reduce the cost to society if you are having fewer treatments in a given time period. 12:03:38 12:03:40 12:03:45 12:03:51 12:03:57

BY MS. CHACON: 12:03:57

Q Now, when you say that "more durable therapies, in the setting of using an anti-VEGF, means having the ability to give treatment less frequently without sacrificing visual acuity," what do you mean by "sacrificing visual acuity"? 12:03:57 12:04:07 12:04:11 12:04:14 12:04:17

A For example, you could have a therapy that you say you are going to get once a year, and that would certainly decrease the burden on patients, caregivers, and physicians, but would 12:04:26 12:04:28 12:04:31 12:04:33

likely be associated with substantial vision loss. That would be sacrificing visual acuity when trying to have a more durable therapy. 12:04:37 12:04:39 12:04:44

Q So is there a particular level of sacrificed visual acuity that you'd be willing to tolerate for decreasing the frequency of treatment? 12:04:51 12:04:57 12:05:00 12:05:06

MS. KAYALI: Objection. Vague. Incomplete hypothetical. 12:05:08 12:05:11

You can answer. 12:05:13

THE WITNESS: It really depends on so many variables. 12:05:19 12:05:20

BY MS. CHACON: 12:05:21

Q Like what? Give me some examples. 12:05:21

A Could you repeat the question, because I was thinking of one as you were saying it, and I want to come back to that. 12:05:32 12:05:33 12:05:35

Q Sure. And just to give you some more context, I'm trying to understand -- it sounds like to me that there's a balance; right, of what you might be willing to tolerate in terms of sacrificed visual acuity versus the benefit of 12:05:37 12:05:39 12:05:41 12:05:44 12:05:46

reducing treatment. 12:05:49

So I want to understand, is there a 12:05:52

particular level of sacrificed visual acuity that 12:05:55

you'd be willing to tolerate for decreasing the 12:05:59

frequency of treatment? 12:06:02

A Thank you. 12:06:04

MS. KAYALI: Objection. Vague. Lacks 12:06:05

foundation. And incomplete hypothetical. 12:06:06

You can answer. 12:06:08

THE WITNESS: So visual acuity outcomes 12:06:09

are paramount. Having a visual acuity difference 12:06:12

that, on average for a group is less than four 12:06:18

letters would equate to something that I and my 12:06:21

patients would be willing to sacrifice. 12:06:25

But short of that, we would continue 12:06:32

monthly or bimonthly injections if it meant that 12:06:35

you might be sacrificing, on average for a group 12:06:38

of four or more letters of visual acuity. 12:06:42

BY MS. CHACON: 12:06:46

Q Is four or more levels of visual acuity 12:06:46

a standard set forth in the field, or is that just 12:06:51

your personal tolerance level for sacrificed 12:06:55

visual acuity? 12:06:59

A It's a standard in the field as it's 12:07:01

accepted as the lower bounds of a non-inferiority 12:07:04

trial, and it also is a standard that I'm very 12:07:06

comfortable with as that average equates to the 12:07:14

percentage of people, for example, that might lose 12:07:16

ten or more letters of vision, two or more lines 12:07:19

on a standard eye chart. 12:07:23

That's about the minimum I would accept 12:07:24

and my patients would accept and my colleagues 12:07:29

would accept. 12:07:32

Q Okay. Would you agree, then, that it is 12:07:33

a balance between making sure that a patient has 12:07:37

sufficient visual acuity and also reducing 12:07:42

treatment burden? 12:07:47

MS. KAYALI: Objection. Incomplete 12:07:49

hypothetical. Lacks foundation. Vague. 12:07:51

You can answer. 12:07:55

THE WITNESS: Again, it depends on so 12:08:01

many parameters, and if one were to give fewer 12:08:02

injections, one would want to be confident that 12:08:10

that outcome did not sacrifice visual acuity 12:08:14

benefits compared with the monthly or bimonthly treatment that you might be given. 12:08:18 12:08:22

BY MS. CHACON: 12:08:24

Q So are you balancing those two considerations? 12:08:24 12:08:26

MS. KAYALI: Objection. Asked and answered. Vague. 12:08:27 12:08:29

THE WITNESS: Again, I'm taking into consideration, among many other parameters, the need for decreased injection frequency to have visual acuity outcomes that are not worse than monthly or bimonthly treatments. 12:08:39 12:08:40 12:08:43 12:08:53 12:09:01

BY MS. CHACON: 12:09:08

Q And I would assume, and correct me if I'm wrong, that safety goes into that mix as well? 12:09:08 12:09:10

MS. KAYALI: Objection. Vague. Incomplete hypothetical. 12:09:14 12:09:17

You can answer. 12:09:18

THE WITNESS: Safety is also a consideration. 12:09:23 12:09:24

BY MS. CHACON: 12:09:25

Q What else would you consider? 12:09:25

MS. KAYALI: Objection. Vague. 12:09:29

THE WITNESS: I would have to think 12:09:36

about it. One that comes to mind is cost. 12:09:37

BY MS. CHACON: 12:09:39

Q Any other considerations that come to 12:09:39

mind? 12:09:44

MS. KAYALI: Objection. Vague. 12:09:44

THE WITNESS: I would have to consider. 12:09:48

That's all that I consider right now. 12:09:49

BY MS. CHACON: 12:09:53

Q Okay. So at least, sitting here today, 12:09:53

would you agree that there is some balancing that 12:09:57

goes on for a patient in their treatment in 12:10:00

between visual acuity, injection, treatment 12:10:04

burden, safety, and cost? 12:10:10

MS. KAYALI: Objection. Incomplete 12:10:13

hypothetical. Vague. 12:10:15

You can answer. 12:10:17

THE WITNESS: Again, it really depends 12:10:20

on the details of all of those parameters. 12:10:21

BY MS. CHACON: 12:10:24

Q But those are parameters that come to 12:10:24

mind today that you would consider in balancing what to give a patient. 12:10:27 12:10:31

Is that fair? 12:10:33

MS. KAYALI: Sorry. Objection. Lacks foundation. Incomplete hypothetical. And vague. 12:10:34 12:10:36

You can answer. 12:10:39

THE WITNESS: Those parameters come into balancing what to give a patient. 12:10:44 12:10:46

BY MS. CHACON: 12:10:48

Q So I want to turn back to the '036 patent and turn back to the claims, which are on page 78 of the -- Exhibit 1001. 12:10:48 12:10:55 12:11:01

Do you understand, generally speaking, Dr. Bressler, that claims define the invention? 12:11:11 12:11:13

MS. KAYALI: Objection. Calls for a legal conclusion. 12:11:17 12:11:17

THE WITNESS: I have a general understanding that it relates to the invention, but, again, it's a legal standard that -- I would have to defer to legal experts on that. 12:11:22 12:11:23 12:11:27 12:11:30

BY MS. CHACON: 12:11:36

Q Okay. When you were evaluating 12:11:36

"obviousness" in your opinions, were you looking at the claims, or were you looking at the specification of the '036 patent? 12:11:43 12:11:47 12:11:50

MS. KAYALI: Objection. Lacks foundation. 12:11:52 12:11:53

THE WITNESS: When I was looking at obviousness, I was applying the legal standards as they were explained to me in my declaration. 12:12:17 12:12:18 12:12:23

BY MS. CHACON: 12:12:28

Q Okay. So those legal standards, that's in Section 3 of your declaration; correct? 12:12:28 12:12:31

A That's correct. 12:12:35

Q Okay. And so all the legal standards that you are applying in your analysis of the facts and the evidence, those were supplied to you by counsel? 12:12:35 12:12:38 12:12:46 12:12:48

A The legal standards that I applied were provided to me by counsel for the opinion that I provided in the declaration. 12:12:50 12:12:52 12:12:56

Q Okay. So just to be clear, you didn't have any familiarity with these concepts or bring your own knowledge to bear on what these legal 12:12:58 12:13:00 12:13:03

concepts mean? 12:13:05

A That is -- 12:13:07

MS. KAYALI: Objection. Foundation. 12:13:10

You can answer. 12:13:10

THE WITNESS: That is correct. 12:13:10

BY MS. CHACON: 12:13:11

Q All right. Let's go back to the claims. 12:13:11

Now, I think you've read Claim 1 to me 12:13:18

earlier, Doctor, so I'm going to have you focus on 12:13:21

Claim 1. Just let me know when you have it in 12:13:24

front of you. 12:13:26

A Okay. One moment. 12:13:27

Q Go ahead and take another look at what 12:13:28

it says. 12:13:33

A Okay. Thank you. 12:14:01

Q Sure. Do the claims state anything 12:14:01

about demonstration of superior efficacy as 12:14:04

compared to the 2-mg dose of aflibercept? 12:14:09

MS. KAYALI: Objection. Calls for a 12:14:15

legal conclusion. 12:14:16

BY MS. CHACON: 12:14:26

Q And just to be clear, Doctor, when I say 12:14:26

"claims," I should say does Claim 1 state anything about superior efficacy over 2 mg of aflibercept? 12:14:29 12:14:34

MS. KAYALI: Objection. Calls for a legal conclusion. 12:14:38 12:14:39

You can answer. 12:14:40

THE WITNESS: So now can you just repeat the question, because I wanted to read it to try to answer your question. 12:14:50 12:14:51 12:14:55

BY MS. CHACON: 12:14:56

Q Does Claim 1 state anything about superior efficacy as compared to 2 mg of aflibercept? 12:14:56 12:14:59 12:15:03

MS. KAYALI: Objection. Calls for a legal conclusion. 12:15:04 12:15:04

You can answer. 12:15:04

THE WITNESS: I don't see any discussion in Claim 1 about 2 mg of aflibercept. 12:15:09 12:15:10

BY MS. CHACON: 12:15:13

Q Does Claim 1 say anything about superior safety over 2 mg of aflibercept? 12:15:13 12:15:20

MS. KAYALI: Objection. Calls for a legal conclusion. 12:15:23 12:15:25

You can answer. 12:15:26

THE WITNESS: I don't see anything in 12:15:31
Claim 1 about aflibercept 2-mg. 12:15:31
BY MS. CHACON: 12:15:36
Q Okay. And do you see anything about 12:15:36
safety in Claim 1? 12:15:42
MS. KAYALI: Objection. Calls for a 12:15:45
legal conclusion. 12:15:46
You can answer. 12:15:47
THE WITNESS: I don't see the word 12:15:53
"safety," but I'm not familiar, from a legal 12:15:54
standpoint, what the method of treating an 12:15:57
angiogenic eye disorder in a human subject in need 12:15:58
thereof since safety is a consideration that we 12:16:01
have when treating an angiogenic eye disorder. 12:16:03
BY MS. CHACON: 12:16:08
Q When considering these claims, did you 12:16:08
go back to the specification to see if it provides 12:16:10
any guidance or definition or anything of that 12:16:13
nature to help your understanding? 12:16:16
MS. KAYALI: Objection. Vague. 12:16:19
You can answer. 12:16:20

THE WITNESS: The term "specification," again, sounds like a legal term that I'm not readily familiar with. 12:16:25 12:16:27 12:16:29

BY MS. CHACON: 12:16:32

Q Sorry. The -- the body of the patent, the "disclosure" is another term for it, perhaps. 12:16:32 12:16:34

A Uh-huh. Okay. So now please repeat the question. 12:16:37 12:16:39

Q When considering these claims, did you go back to the body of the patent or the disclosure to see if it provides any guidance or definition of that nature to help your understanding of the claims? 12:16:39 12:16:41 12:16:43 12:16:46 12:16:51

MS. KAYALI: Objection. Vague. Calls for a legal conclusion. 12:16:52 12:16:55

You can answer. 12:16:59

THE WITNESS: I'm not familiar enough with the terms you're using to be able to clearly answer the question. 12:17:03 12:17:04 12:17:07

BY MS. CHACON: 12:17:07

Q And just going back to Claim 1 for a moment. Is there anything in claim 1 requiring 12:17:07 12:17:10

increased durability as compared to 2 mg of aflibercept? 12:17:16 12:17:20

MS. KAYALI: Objection. Calls for a legal conclusion. 12:17:23 12:17:23

You can answer. 12:17:24

THE WITNESS: Again, I'm not clear if -- when stating a method for treating an angiogenic eye disorder in a human subject in need thereof if that's including the need for a greater durability or greater efficacy for visual acuity. 12:17:28 12:17:29 12:17:33 12:17:37 12:17:40

BY MS. CHACON: 12:17:44

Q Okay. But you don't -- for example, you don't see the word "durability" anywhere in Claim 1, can we agree on that? 12:17:44 12:17:48 12:17:52

A We can agree there's no "durability" word in Claim 1. 12:17:56 12:18:00

Q Now, I won't -- I'm not going to do that for all of these claims -- 12:18:01 12:18:04

A Thank you. 12:18:06

Q I'll spare us -- spare us both from that, but one can look at any one of these claims and go through the same exercise that we just did 12:18:08 12:18:10 12:18:13

to see whether or not it said anything about increased efficacy, safety, or durability. 12:18:17 12:18:19

Would you agree we can do that if we had unlimited time? 12:18:22 12:18:25

MS. KAYALI: Objection. Vague. Incomplete hypothetical. 12:18:26 12:18:28

Are you asking the witness to do that? 12:18:29

MS. CHACON: I just said I wasn't going to ask him to do that. I was just asking him if we can go through that process if we decided to spend the time to do it, but we're not going to. 12:18:32 12:18:33 12:18:36 12:18:39 12:18:40

BY MS. CHACON: 12:18:41

Q So do you agree, we can just look at the rest of the claims and see if they have those words that we just -- the process that we went through for Claim 1? 12:18:41 12:18:45 12:18:45 12:18:46

MS. KAYALI: Objection. Vague. 12:18:49

THE WITNESS: That's vague. I'm not sure what process you're talking about through Claim 1. I'm happy to look through these for a word that you're looking for. 12:18:50 12:18:51 12:18:54 12:18:58

BY MS. CHACON: 12:19:00

Q That's fine. We don't need to spend time doing that. And I just want to clarify, Dr. Bressler, because I believe in your declaration you stated that each of the claims of the '036 patent get -- or recite at least about -- or about 8 mg. 12:19:00 12:19:03 12:19:48 12:19:51 12:20:00 12:20:05

Do you recall stating that in your declaration? 12:20:07 12:20:09

A I do recall discussing the word "about." 12:20:17

Q And for what it's worth, check paragraph 233 in your declaration, which is on page 127. 12:20:21 12:20:25 12:20:28

A Okay. I'm there. 12:20:58

Q Okay. And I just want to confirm that it's your understanding that each of the claims includes at least about 8 mg of aflibercept. 12:20:59 12:21:00 12:21:04

Did I understand your position in paragraph 233 correctly? 12:21:10 12:21:11

MS. KAYALI: Objection. Vague. 12:21:18

THE WITNESS: When you said "each of the claims," I'm not sure that each of the claims say 12:21:27 12:21:28

"about 8 mg." 12:21:35

BY MS. CHACON: 12:21:37

Q I'm just going off of what you included, 12:21:37

Doctor, in paragraph 233. You state, "Every 12:21:40

challenged claim of the '036 patent recites a 12:21:44

method for treating comprising of administering a 12:21:46

dose of about 8 mg of aflibercept;" is that 12:21:50

correct? 12:21:52

A That is correct. 12:21:52

Q Okay. And I just want to make sure that 12:21:53

we're clear on some of the nuances here. So 12:21:56

Claim 1, which we were looking at, that claims "at 12:21:59

least about 8 mg of a VEGF receptor fusion 12:22:03

protein" and then it goes on. 12:22:06

Do you see that? 12:22:10

A I see that paragraph. 12:22:31

Q Okay. And when it says "at least 12:22:33

about 8 mg," do you understand 8 mg to be the 12:22:34

lower threshold that's considered in that claim? 12:22:39

MS. KAYALI: Objection. Vague. Calls 12:22:46

for a legal conclusion. 12:22:47

You can answer. 12:22:48

THE WITNESS: I would not be able to characterize that -- there was something at the end of your sentence that you said, so you'll have to repeat it again for me to answer. 12:22:53 12:22:55 12:23:03 12:23:05

MS. CHACON: I said "lower threshold." 12:23:07

MS. KAYALI: Sorry. Can you let the witness finish, please? 12:23:08 12:23:10

Go ahead, Dr. Bressler. 12:23:10

THE WITNESS: I just needed the end of the sentence to recall what you had asked. 12:23:11 12:23:13

BY MS. CHACON: 12:23:14

Q Okay. So based on your review of Claim 1, what do you understand "at least about 8 mg" to mean? 12:23:15 12:23:20 12:23:24

A I would conclude that it means, as I said in paragraph 233 of my declaration, "Every challenged claim of the '036 patent recites a method for treating an angiogenic eye disorder comprising administering a dose of at least about 8 mg of aflibercept." 12:23:45 12:23:46 12:23:51 12:23:55 12:23:59 12:23:59

Q All right. So when you look at that, does that tell you -- when you see "at least 12:24:03 12:24:05

about 8 mg," does that tell you that it's -- it could also mean 9 mg, something more than 8 mg? 12:24:08 12:24:14

MS. KAYALI: Objection. Calls for a legal conclusion. Vague. 12:24:22 12:24:23

You can answer. 12:24:26

THE WITNESS: I would say it is administering a dose of at least about 8 mg of aflibercept. 12:24:30 12:24:32 12:24:36

BY MS. CHACON: 12:24:37

Q Right. So that means 8 or more? 12:24:37

MS. KAYALI: Objection. Vague. 12:24:46

THE WITNESS: I did not say 8 or more. I said at least about 8 mg of aflibercept. 12:24:53 12:24:55

BY MS. CHACON: 12:24:59

Q Okay. And I'm not -- maybe we'll put it in context. So if you take a look at Claim 31, for example, in the middle of Claim 31, it says "about 8 mg of aflibercept." Okay? 12:24:59 12:25:02 12:25:05 12:25:10

So I'm trying to understand what your understanding is of the dose limitations that are included in Claim 1 versus Claim 31. Okay? 12:25:15 12:25:17 12:25:21

So Claim 1 says, "At least about 8 mg." 12:25:24

Claim 31 says, "About 8 mg." And my question to you is: Do you understand those to be the same thing? Do you understand them to be something different? And if so, what's the difference? 12:25:29 12:25:34 12:25:36 12:25:38

MS. KAYALI: Objection. Calls for a legal conclusion. Vague. 12:25:42 12:25:43

You can answer. 12:25:45

THE WITNESS: I don't have the legal experience in patents to be able to explain how "at least about 8 mg" in Claim 1 relates to "about 8 mg" in Claim 31. 12:25:49 12:25:50 12:25:56 12:26:02

BY MS. CHACON: 12:26:05

Q And again, I'm not asking from a legal perspective. I'm asking from your expertise as a clinician who's providing opinions from the perspective of a person of ordinary skill in the art. 12:26:05 12:26:08 12:26:11 12:26:14 12:26:19

So from a person of ordinary skill in the art's perspective, what would that person understand, "at least about 8 mg to be" versus "about 8 mg"? 12:26:19 12:26:19 12:26:21 12:26:25

MS. KAYALI: Objection. Calls for a 12:26:30

legal conclusion. 12:26:31

You can answer. 12:26:34

THE WITNESS: I think that POSA would go to a patent lawyer and ask them to explain what those two different phrases mean. 12:26:35 12:26:39 12:26:41

BY MS. CHACON: 12:26:45

Q So sitting here today, do you have any understanding as to whether or not those two things are different or the same? 12:26:45 12:26:51 12:26:53

MS. KAYALI: Objection. Vague. 12:26:55

THE WITNESS: From a patent point of view, I would need or seek out a patent lawyer to help explain to me whether those are different or the same. 12:27:01 12:27:05 12:27:11 12:27:15

BY MS. CHACON: 12:27:16

Q Okay. Did you do that? Did you ask counsel for any explanation as to whether or not those were the same or different? 12:27:16 12:27:19 12:27:22

And I'm asking because, if they're different, that might make a difference in terms of your analysis. If they're the same, maybe it doesn't. So I'm asking if you asked for that 12:27:24 12:27:27 12:27:30 12:27:33

clarification. 12:27:35
MS. KAYALI: Objection. Lacks 12:27:35
foundation. And I'll instruct the witness not to 12:27:37
reveal the substance of any privileged 12:27:39
communications. 12:27:41
THE WITNESS: So I would not be able to 12:27:44
answer that without talking about what we 12:27:46
discussed. 12:27:48
BY MS. CHACON: 12:27:49
Q All right. So let's hold onto the '036 12:27:49
patent. We'll need it in a little bit, but you 12:28:26
can put it to the side for now. 12:28:29
All right, Doctor. I want to ask you 12:28:51
some questions about the Vitti reference. Now, I 12:28:54
think when we looked at the grounds earlier today, 12:29:03
Vitti was included in Ground 1. 12:29:06
Do you recall us reviewing that? 12:29:10
A I do recall our mentioning that. 12:29:16
Q And I think -- 12:29:18
(Simultaneous speakers.) 12:29:19
BY MS. CHACON: 12:29:19
Q Sorry. And I think you told me you had 12:29:19

reviewed the Vitti reference in preparation for your deposition today; is that correct? 12:29:22 12:29:24

A I have reviewed it. 12:29:27

Q Okay. And just generally speaking, what do you understand the Vitti reference to be teaching? 12:29:28 12:29:40 12:29:41

MS. KAYALI: Objection. Vague. 12:29:47

THE WITNESS: The -- my understanding of the Vitti reference is how I've outlined starting on page 87 of my declaration. 12:29:58 12:30:00 12:30:04

BY MS. CHACON: 12:30:18

Q Okay. So is your complete understanding of the Vitti reference articulated in Section 2 that starts on page 87 of your declaration? 12:30:18 12:30:21 12:30:24

MS. KAYALI: Objection. Lacks foundation. 12:30:27 12:30:28

You can answer. 12:30:30

Vague. 12:30:31

You can answer. 12:30:32

THE WITNESS: My understanding of how Vitti relates to whether a POSA would pursue an 8-mg aflibercept dose is outlined in the 12:30:41 12:30:42 12:30:51

declaration here. 12:30:53
BY MS. CHACON: 12:30:54
Q And I just want to point you to 12:30:54
paragraph 166 in that section. And you state, 12:30:58
"Though Dr. D'Amico does not reference the 12:31:07
disclosure when discussing the 8 mg disclosure, he 12:31:07
nonetheless states that Vitti teaches formulations 12:31:11
with a 'at least about 8 mgs' or 'about 8 mgs' 12:31:14
primarily because of Vitti's concentration 12:31:21
disclosures." 12:31:25
Do you see that? 12:31:27
A I do see that. 12:31:28
Q All right. So when you wrote that, did 12:31:29
you have an understanding of "at least about 8 12:31:31
mgs" and "about 8 mgs" meant? 12:31:33
MS. KAYALI: Objection. Vague. Lacks 12:31:40
foundation. 12:31:42
You can answer. 12:31:42
THE WITNESS: I don't have an 12:31:54
explanation of "at least about 8 mgs" or "about 8 12:32:02
mgs" except that both of those are mentioned in 12:32:06
Vitti. 12:32:10

BY MS. CHACON: 12:32:10

Q Turning to paragraph 165, you opine -- 12:32:10

A I would like to just -- as I was thinking about it -- 12:32:22 12:32:25

Q Uh-huh. 12:32:27

A I don't think Vitti mentioned 8 mg when I just said that. 12:32:28 12:32:31

Q Okay. And how does that inform your understanding of "at least about 8 mgs" or about "8 mgs," if it does? 12:32:34 12:32:37 12:32:41

MS. KAYALI: Objection. Vague. Calls for a legal conclusion. 12:32:55 12:32:56

You can answer. 12:33:00

THE WITNESS: I understand, as I said on page 89 at the bottom, that Vitti defines the term about when used in reference to a particular recited numerical value means that the value may vary from the recited value by no more than 1 percent. 12:33:18 12:33:19 12:33:22 12:33:25 12:33:29 12:33:30

For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between. 12:33:30 12:33:32 12:33:37

BY MS. CHACON: 12:33:38

Q Okay. So the portion that you just read to me is Vitti's definition of the term "about." Is that correct? 12:33:38 12:33:41 12:33:46

A That is correct. 12:33:47

Q Okay. And I was asking you about how the term "about" is used in the '036 patent. Did you understand that? 12:33:47 12:33:54 12:33:59

MS. KAYALI: Objection. Vague. 12:34:05

THE WITNESS: I was thinking about your previous question and then discussing Vitti's definition of "about." 12:34:13 12:34:15 12:34:18

BY MS. CHACON: 12:34:19

Q Okay. Let's turn to paragraph 165. And towards the middle of the -- well, let's start at the beginning. 12:34:19 12:34:32 12:34:35

In the second sentence, you say, "In my opinion, the only dose of aflibercept Vitti explicitly discloses is two mgs" and with some citation there. 12:34:39 12:34:42 12:34:43 12:34:49

And then you say after that, "The disclosed range of '.05 mgs to about 10 mgs' of a 12:34:52 12:34:55

VEGF antagonist contains nearly a thousand discreet aflibercept doses in .01-mg increments or nearly 200 in .05-mg increments." 12:35:03 12:35:08 12:35:14

Do you see that? 12:35:16

A I do. 12:35:18

Q Okay. How did you determine that? 12:35:18

MS. KAYALI: Objection. Vague. 12:35:28

THE WITNESS: How did I determine that it contains nearly a thousand discreet doses in .01-mg increments? 12:35:34 12:35:35 12:35:37

BY MS. CHACON: 12:35:41

Q Correct. 12:35:41

A Mathematically. 12:35:42

Q What do you mean by that? 12:35:44

A If you go in .01 increments from .05 to 10, that's going to be almost a thousand discreet doses. 12:35:46 12:35:52 12:35:57

Q Okay. And so why did you select .01-mg increments versus .05-mg increments versus .1-mg increments? 12:35:58 12:36:02 12:36:10

MS. KAYALI: Objection. Foundation. 12:36:11

THE WITNESS: As I said in the last 12:36:15

sentence, I was informed by counsel that there's no presumption of obviousness when the prior art range is so broad as to encompass a very large number of possible distinct compositions, as in .01 a thousand or if we go to .05-mg, 200 increments. 12:36:16 12:36:19 12:36:23 12:36:28 12:36:30 12:36:35

BY MS. CHACON: 12:36:37

Q So how does that last sentence inform your selection, as a person of skill in the art, of what increments fall within the range of .05 mgs to about 10 mgs of a VEGF antagonist as disclosed in Vitti? 12:36:37 12:36:40 12:36:42 12:36:47 12:36:55

MS. KAYALI: Objection. Foundation. Vague. 12:36:57 12:36:58

THE WITNESS: I have a general understanding that people could formulate in these increments that I gave at .01-mg or .05-mg. 12:37:04 12:37:05 12:37:17

BY MS. CHACON: 12:37:24

Q What's your general understanding based on? 12:37:24 12:37:26

A I believe it's likely without being a formulator that those increments are not so tiny 12:37:29 12:37:41

that they could not be achieved. 12:37:48

Q And you told me earlier, Dr. Bressler, 12:37:50

that you are not a formulator; correct? 12:37:54

A I'm not a formulator. 12:37:57

Q You don't have any expertise in 12:37:59

formulation? 12:38:02

A I do not have any expertise in 12:38:03

formulation. 12:38:04

Q And you had access to a formulator; 12:38:04

right? Dr. Trout? 12:38:07

MS. KAYALI: Objection. 12:38:10

THE WITNESS: I did not have access to 12:38:11

Dr. Trout. 12:38:13

BY MS. CHACON: 12:38:13

Q You had two calls with him in June, 12:38:13

June 10th and June 12th; correct? 12:38:17

A I did. 12:38:20

Q Okay. And he is a formulator; correct? 12:38:21

A He is a formulator. 12:38:24

Q And he's providing opinions in this 12:38:25

matter from the perspective of a formulator; 12:38:27

right? 12:38:29

MS. KAYALI: Objection. Lacks foundation. 12:38:30 12:38:32

THE WITNESS: I presume so. I don't know what he formulated in terms of opinions. 12:38:32 12:38:34

BY MS. CHACON: 12:38:36

Q Okay. And you said during your June 10th and June 12th meetings that you didn't have any questions for Dr. Trout; is that correct? 12:38:36 12:38:38 12:38:43

A That is correct. 12:38:46

Q So you didn't ask him whether assuming a thousand discreet increments -- or a thousand discreet aflibercept doses in .01-mg increments or nearly 200 in .05-mg increments was feasible from a formulation perspective? 12:38:46 12:38:50 12:38:50 12:38:55 12:38:59

MS. KAYALI: Objection. Lacks foundation. Vague. 12:39:01 12:39:02

THE WITNESS: I did not ask him that. 12:39:07

BY MS. CHACON: 12:39:09

Q Did you consult any other literature to support whether or not formulating in those kind of increments was feasible? 12:39:09 12:39:17 12:39:20

A I did not consult any other literature. 12:39:24

Q I'm going to introduce what's already been marked in this proceeding as Alvotech Exhibit 1007. It's the Vitti patent application publication. 12:39:38 12:39:40 12:39:44 12:39:46

(Petitioner's Exhibit 1007 was marked for identification, the original of which is attached hereto.) 12:39:52 12:39:52 12:39:52

MS. KAYALI: And, Counsel, I'm conscious that we're turning to -- well, I don't know if it's a new subject or at least a new exhibit, and we've been going just shy of an hour. So it might be a good time for a lunch break. 12:39:55 12:39:55 12:39:56 12:39:59 12:40:02

MS. CHACON: Yeah, no, we're going to finish the question, because it's directly related to what we were just talking about. 12:40:04 12:40:05 12:40:06

So let's get through these next couple of questions, and then we can take a break. 12:40:06 12:40:09

MS. KAYALI: Well, I'll defer to Dr. Bressler. 12:40:12 12:40:13

Would you like to take a break now, Dr. Bressler? 12:40:14 12:40:14

THE WITNESS: Can we take a break now 12:40:16

and come back to that? I'd rather be fresh. 12:40:17

BY MS. CHACON: 12:40:19

Q So you -- I really just have one 12:40:19

question for you, Doctor. Do you want to indulge 12:40:22

me a question, and then we can break for lunch? 12:40:24

A I'm happy to answer one question. 12:40:28

Q All right. All right. So I've handed 12:40:31

you what's been -- I think I said previously 12:40:32

introduced as Alvotech Exhibit 1007, which is the 12:40:37

Vitti patent publication. 12:40:41

MS. KAYALI: Do you have Exhibit 1007, 12:40:58

Dr. Bressler? 12:41:00

THE WITNESS: I do. 12:41:02

MS. KAYALI: Okay. Then this must be my 12:41:03

copy. 12:41:05

BY MS. CHACON: 12:41:10

Q All right. So I'm going to point your 12:41:10

attention to paragraph 139 in Vitti, which is 12:41:12

page 21 in the document. 12:41:15

A Okay. Thank you. What paragraph? 12:41:54

Q Paragraph 139, please -- 12:41:56

A Okay. 12:41:58

Q -- in Vitti. 12:41:58

A Okay. Thank you. 12:42:03

Q Of course. And you'll see in 12:42:04

paragraph 139 it discloses the range of .05 mgs to 12:42:06

about 10 mgs above VEGF antagonist, (ergo 12:42:12

aflibercept.) 12:42:16

Do you see that? 12:42:16

MS. KAYALI: Objection. Lacks 12:42:17

foundation. 12:42:18

THE WITNESS: Paragraph 139? 12:42:28

BY MS. CHACON: 12:42:29

Q Yes. 12:42:29

A I see that. 12:42:30

Q Okay. Now -- 12:42:31

MS. KAYALI: Okay. Sorry. You said one 12:42:32

question. Are we going to continue? I need to 12:42:33

take a break. 12:42:36

MS. CHACON: I'm going to ask this last 12:42:36

question, Counsel. I'm going to ask you to just 12:42:39

indulge this last question. 12:42:39

MS. KAYALI: You told me you were going 12:42:40

to ask one question, then we said we were going to 12:42:41

take a break. 12:42:43

Dr. Bressler said he'd indulge you one 12:42:44

question, then we were going to take a break. 12:42:45

We're taking a break. 12:42:45

MS. CHACON: I'm asking him where he is 12:42:47

in the document, Counsel. I'm going to ask my 12:42:49

question. 12:42:51

BY MS. CHACON: 12:42:51

Q Dr. Bressler, is there any -- 12:42:51

MS. KAYALI: Dr. Bressler, would you 12:42:52

like a break? 12:42:53

BY MS. CHACON: 12:42:54

Q Is there anywhere in this paragraph, 12:42:54

Dr. Bressler, where Vitti identifies the 12:42:57

increments in between the range of .05 mgs to 12:42:58

about 10 mgs of a VEGF antagonist, ergo 12:42:59

aflibercept? 12:43:02

MS. KAYALI: You can answer that 12:43:05

question, Dr. Bressler. 12:43:06

And then we're going off the record, 12:43:08

Counsel. 12:43:09

THE WITNESS: In this paragraph 139, it 12:43:10

does not state what discreet aflibercept doses increments are being considered. 12:43:27 12:43:35

MS. CHACON: We can go off the record. 12:43:46

MS. KAYALI: Okay. 12:43:47

THE VIDEOGRAPHER: We are going off the record. The time is 12:43. 12:43:49 12:43:50

(Lunch recess.) 12:43:56

12:43:56

Washington, D.C., Thursday, September 10, 2026 12:43:56

(Afternoon Session) 12:43:56

12:43:56

THE VIDEOGRAPHER: We are going back on the record. The time is 13:28. 13:28:36 13:28:38

BY MS. CHACON: 13:28:40

Q Welcome back, Dr. Bressler. 13:28:40

A Thank you. 13:28:43

Q During any of the breaks today or during lunch, did you speak with counsel about the substance of your testimony at all? 13:28:44 13:28:46 13:28:48

A No, not at all. 13:28:49

Q All right. Earlier today we were talking about various characteristics of anti-VEGF treatments, things like efficacy, safety, durability. 13:28:56 13:28:59 13:29:02 13:29:09

Do you recall some of that discussion this morning? 13:29:10 13:29:12

A I do. 13:29:13

Q Okay. And I want to talk to you a little bit about safety in the concept of overdosage. 13:29:13 13:29:15 13:29:18

So from your perspective as a clinician, maybe even coming into this proceeding, what is your general understanding of what an overdosage is? 13:29:20 13:29:22 13:29:26 13:29:31

MS. KAYALI: Objection. Vague. 13:29:32

You can answer. 13:29:33

THE WITNESS: My general understanding would be that an overdosage is giving more of a dosage than you were planning to give. 13:29:34 13:29:36 13:29:39

BY MS. CHACON: 13:29:42

Q So let's say -- let's put the setting in clinical practice -- right? -- where you are using FDA-approved drugs. 13:29:42 13:29:53 13:29:56

Is an overdosage planning to give more than what would -- the dose that's FDA-approved? 13:29:57 13:29:59 13:30:03

MS. KAYALI: Objection. Asked and answered. Vague. 13:30:05 13:30:05

THE WITNESS: With anti-VEGF agents, specifically, overdosage to me would be anything that is more than what you were planning to give based on the agent that was being provided. 13:30:12 13:30:20 13:30:24 13:30:27

BY MS. CHACON: 13:30:33

Q And so, in your clinical practice, do you give your patients dosages of anti-VEGF drugs that are different from what they've been FDA-approved for? 13:30:33 13:30:40 13:30:48 13:30:50

MS. KAYALI: Objection. Vague. Compound. 13:30:51 13:30:53

You can answer. 13:30:53

THE WITNESS: I'm extremely careful to give exactly the dosage that is in the FDA label intended, for example, if I'm using a syringe that I want to prime .05ML, I'm extremely careful to get that primed right to .05ML; not a little above; not a little below. 13:30:58 13:31:03 13:31:14 13:31:22 13:31:29 13:31:30

If I'm using a prefilled syringe, I'm extremely careful to get that plunger right to where it's supposed to be, which is why I said earlier in the day, I looked at the product insert to understand exactly where that plunger should be to give the exact amount that's being planned. 13:31:31 13:31:34 13:31:37 13:31:39 13:31:42 13:31:46

So it's very specific with anti-VEGF agents. 13:31:50 13:31:54

BY MS. CHACON: 13:31:54

Q And would you say others in the field 13:31:55

are very precise like you are when delivering 13:31:57

these types of drugs into the eye? 13:32:00

MS. KAYALI: Objection. Calls for 13:32:05

speculation. 13:32:06

You can answer. 13:32:07

THE WITNESS: I anticipate that would be 13:32:08

the standard response. We have not had 13:32:09

presentations where people talk about using more 13:32:13

unless they had a complication, and then they -- 13:32:17

they then present that. 13:32:20

BY MS. CHACON: 13:32:23

Q Okay. And so, because you are so 13:32:23

careful to be right on the dot for the particular 13:32:27

volume that you're injecting, would you believe it 13:32:30

to be difficult if you were trying to inject, 13:32:36

let's say, a volume of 51 mL as opposed to 50 mL 13:32:41

to get that precision? 13:32:47

A It depends. If I were priming the 13:32:49

syringe, it would be tough. If I was depending on 13:32:53

a manufacturer to give me a line to fill it to 51, 13:32:56

I would trust that they figured out how to get it to 51, not 50, not 52. 13:33:01 13:33:05

Q Okay, but if you were just drawing it up in the -- in the -- from the vile, having that level of precision would be challenging for clinicians if you were trying to get precisely 51 or 52 mL of volume. 13:33:10 13:33:12 13:33:12 13:33:14 13:33:17

Would you agree with that? 13:33:21

MS. KAYALI: Pardon me. Objection. Lacks foundation. 13:33:22 13:33:24

You can answer. 13:33:24

THE WITNESS: With the syringes that we use, it would be challenging to get 51 instead of 50, but I don't think it would be challenging for a manufacturer to provide a prefilled syringe with exactly 51. 13:33:32 13:33:34 13:33:37 13:33:39 13:33:42

BY MS. CHACON: 13:33:43

Q Now, I know we talked earlier about formulation-related issues, and when it comes to a needle, a prefilled syringe, perhaps, have you ever asked a manufacturer to manufacture a particular volume in a prefilled syringe for you 13:33:43 13:33:47 13:33:53 13:33:58 13:34:01

to clinically administer to your patients? 13:34:06

MS. KAYALI: Objection. Vague. 13:34:10

THE WITNESS: I don't recall asking a 13:34:26

manufacturer except when biosimilars were being 13:34:27

developed by Samsung -- 13:34:43

MS. KAYALI: And I'll caution the 13:34:45

witness not to reveal the content of any 13:34:46

confidential third-party information. 13:34:48

If you can answer that without doing so, 13:34:51

you should feel free. 13:34:53

THE WITNESS: I'm going to end my 13:34:55

"except" right there. 13:34:59

BY MS. CHACON: 13:35:01

Q Fair enough. 13:35:01

Just to be clear, for your clinical 13:35:09

practice, have you ever asked a manufacturer to 13:35:11

make a specialized prefilled syringe for you 13:35:13

that had a volume of, you know, a 1-mL 13:35:16

increment? 13:35:20

MS. KAYALI: Again, without revealing 13:35:22

the identity of confidential information of any 13:35:23

third party, you can answer that. 13:35:26

1	THE WITNESS: So now could you just	13:35:32
2	please repeat the question?	13:35:34
3	BY MS. CHACON:	13:35:35
4	Q Have you ever asked a manufacturer to	13:35:35
5	make a specialized prefilled syringe for you that	13:35:37
6	had a volume of a 1 mL increment?	13:35:40
7	MS. KAYALI: Objection. Vague.	13:35:46
8	THE WITNESS: In general, any	13:35:55
9	recommendation on setting a prefilled syringe	13:35:59
10	would be to something at an integer level,	13:36:03
11	like, 49, 50, 51, 53. That would be the general	13:36:07
12	approach. It wouldn't be 51.5 or 47.2.	13:36:13
13	BY MS. CHACON:	13:36:17
14	Q Fair enough.	13:36:17
15	But I'm asking, have you ever asked a	13:36:19
16	manufacturer to make a prefilled syringe for your	13:36:21
17	clinical use with your patients that was at the	13:36:24
18	integer level?	13:36:27
19	MS. KAYALI: Objection. Vague.	13:36:29
20	THE WITNESS: For my clinical practice,	13:36:36
21	I cannot recall asking a manufacturer to make a	13:36:38
22	specific prefilled syringe for me.	13:36:41

BY MS. CHACON: 13:36:44

Q Are you aware of any prefilled syringes 13:36:44

that are available for anti-VEGF drugs that have 13:36:51

volumes at the integer level or less? 13:36:56

MS. KAYALI: Objection. Vague. 13:36:59

THE WITNESS: I'm not aware of any. 13:37:03

BY MS. CHACON: 13:37:04

Q Did you search for any in preparing your 13:37:04

opinions in this case? 13:37:09

MS. KAYALI: Objection. Vague. 13:37:11

THE WITNESS: I didn't search for any. 13:37:13

BY MS. CHACON: 13:37:15

Q Now, we were talking a minute ago about 13:37:15

overdosages, which you mentioned you're very 13:37:25

careful to provide the specific amount that FDA 13:37:28

has approved, and if it's something more than 13:37:31

that, then that would be considered an overdose. 13:37:35

Is that your understanding? 13:37:39

MS. KAYALI: Objection. Lacks 13:37:40

foundation. 13:37:40

You can answer. 13:37:41

THE WITNESS: The general term 13:37:46

"overdosage" to me is, with respect to anti-VEGF agents, giving more than what was the intended amount in the label of what I would -- of the agent that I was giving. 13:37:46 13:37:52 13:37:56 13:37:59

BY MS. CHACON: 13:38:01

Q Are there ever any circumstances where you would give a patient less than what the label has recommended? So, for example, less than 2 mg of EYLEA? 13:38:01 13:38:04 13:38:08 13:38:12

A There haven't been any -- 13:38:18

MS. KAYALI: Objection. Compound. 13:38:20

But you can answer. 13:38:21

THE WITNESS: There haven't been any circumstances where I have purposely given less than the recommended dosage. 13:38:22 13:38:23 13:38:29

BY MS. CHACON: 13:38:31

Q Are there any -- well, in the event of an overdose, are there any standard procedures that you're aware of, Dr. Bressler, that a clinician would follow after an overdose? 13:38:31 13:39:02 13:39:05 13:39:08

A I would assume, after an overdose, I would explain to the patient that I just gave them 13:39:18 13:39:20

more than what was intended. 13:39:24

Q And then what would you do? 13:39:28

MS. KAYALI: Objection. Incomplete hypothetical. 13:39:30 13:39:31

THE WITNESS: It really depends on numerable circumstances, if the overdose was tiny versus it was a lot, if the overdose for any reason -- I hypothesize might be of danger to the patient. 13:39:35 13:39:41 13:39:46 13:39:49 13:39:57

So it's really difficult without a specific scenario to say, other than uniformly, I would inform the patient that that occurred. 13:39:57 13:39:59 13:40:03

BY MS. CHACON: 13:40:05

Q Would you monitor the patient after any overdose? 13:40:05 13:40:07

MS. KAYALI: Objection. Incomplete hypothetical. Lacks foundation. 13:40:08 13:40:10

THE WITNESS: Again, it depends on all the parameters of how much the overdose was, was that an overdose because of an increased volume, how much the increased volume was, so, really, it depends on so many parameters. 13:40:14 13:40:16 13:40:20 13:40:29 13:40:31

BY MS. CHACON: 13:40:34

Q Have you ever personally, Dr. Bressler, 13:40:34

administered a patient an overdose of EYLEA or 13:40:41

you gave them more volume than was approved for 13:40:45

the 2-mg dose EYLEA? 13:40:53

MS. KAYALI: Objection. Vague. 13:40:55

You can answer. 13:40:56

THE WITNESS: To my recollection, I've 13:41:02

never purposely given an overdose of any 13:41:03

anti-VEGF. 13:41:10

BY MS. CHACON: 13:41:13

Q Are you aware of any accidental 13:41:13

overdoses of any anti-VEGF injection? 13:41:14

A To my recollection, I'm not aware of any 13:41:19

accidental overdoses of an anti-VEGF injection 13:41:22

that I've given. 13:41:30

Q You mentioned a moment ago an 13:41:42

overdosage, I believe, based on volume. Are there 13:41:43

other overdosages that can occur in your mind? 13:41:48

MS. KAYALI: Objection. Vague. 13:41:56

THE WITNESS: For example, if you 13:42:03

were planning to give 0.3 mL -- sorry -- 0.3 mg 13:42:04

of ranibizumab and you took a preparation that was 0.5 mg and that was not your intention, that would be giving an overdose to that patient that you were not intending without changing the volume because those both come in a volume of 0.5 mL. 13:42:18 13:42:26 13:42:31 13:42:35 13:42:37 13:42:42

BY MS. CHACON: 13:42:45

Q Are you aware of any studies or instances of dose -- overdosage of aflibercept where the volume was kept constant? 13:42:45 13:42:47 13:42:54

MS. KAYALI: Objection. Vague. 13:42:59

THE WITNESS: Could you repeat the question, please? 13:43:02 13:43:03

BY MS. CHACON: 13:43:04

Q Are you aware of any studies that evaluated, or instances of overdosage of aflibercept where the overdosage was based on dose, meaning the volume was kept constant? 13:43:04 13:43:06 13:43:10 13:43:13

MS. KAYALI: Objection. Vague. 13:43:16

THE WITNESS: I'm not aware of any studies where an overdosage was given of aflibercept without changing the volume. 13:43:22 13:43:23 13:43:32

BY MS. CHACON: 13:43:34

Q Did you search for any such examples in 13:43:34

preparing your opinions in your declaration? 13:43:38

MS. KAYALI: Objection. Vague. And 13:43:40

lacks foundation. 13:43:44

THE WITNESS: I did not search for any 13:43:51

studies that purposely gave an overdosage of 13:43:53

aflibercept. 13:44:05

BY MS. CHACON: 13:44:07

Q Maybe not purposely, but what about just 13:44:07

observed? Did you see any studies where that was 13:44:10

observed? Maybe it was by accident? 13:44:13

A So this is a different question than I 13:44:17

understood you to ask earlier. So can you ask the 13:44:19

current question, please? 13:44:21

Q Sure. So you were -- you were 13:44:23

qualifying it by saying, "I haven't seen any 13:44:25

studies where it was purposely given that way," 13:44:29

and I'm just trying to understand if you've seen 13:44:31

any examples where it was not purposely given that 13:44:34

way. 13:44:37

Do you see the difference? 13:44:39

MS. KAYALI: Objection. Vague. 13:44:40

THE WITNESS: So please just ask the 13:44:45

question from the start now. 13:44:46

BY MS. CHACON: 13:44:47

Q Sure. Will do. 13:44:47

Are you aware of any studies that 13:44:49

observed incidental -- instances of overdosage of 13:44:53

aflibercept where the overdosage was based on 13:44:59

dose, meaning the volume was kept constant? 13:45:03

MS. KAYALI: Objection. Vague. 13:45:06

THE WITNESS: I'm not aware of any 13:45:24

studies where that detail was given where the 13:45:25

overdosage was given with or without increasing 13:45:28

the volume. 13:45:36

BY MS. CHACON: 13:45:36

Q Dr. Bressler, I'm going to have the 13:45:36

court reporter hand you what's already been marked 13:46:03

in this proceeding as Exhibit 1009, which is the 13:46:06

EYLEA Australian label. 13:46:15

THE WITNESS: Okay. 13:46:17

(Petitioner's Exhibit 1009 was marked 13:46:30

for identification, the original of which is 13:46:30

attached hereto.) 13:46:30

BY MS. CHACON: 13:47:00

Q Feel free to take a look at 13:47:00

Exhibit 1009, and let me know when you're ready. 13:47:02

A Okay. Okay. Thank you. 13:47:06

Q Of course. All right. So Exhibit 1009 13:48:08

is the Australian label for 2~mg of EYLEA. 13:48:11

Do you see that? 13:48:19

A I do. 13:48:20

Q Okay. I'm going to have you turn to 13:48:21

page 35 of the exhibit, and we're going to take a 13:48:29

look at the overdosage section. Let me know when 13:48:31

you get there. 13:48:34

A Okay. I'm on that page. 13:48:41

Q Sure. So just to confirm, in this 13:48:42

section, it states, "The clinical trial doses of 13:48:47

up to 4 mgs in monthly integrals and isolated 13:48:51

cases of overdoses with 8 mgs were generally well 13:48:57

tolerated." 13:49:02

Do you see that? 13:49:02

A I do see that. 13:49:07

Q And then it goes on to say, "Overdosing 13:49:08

was associated with increased injection volume and subsequently with increased intraocular pressure." 13:49:10 13:49:11

Do you see that next sentence? 13:49:19

A I do. 13:49:20

Q Okay. Dr. Bressler, do you understand the label to be reporting here that the overdose that was caused in the four-month monthly intervals -- or I'm sorry -- the 8 mg overdoses were due to increased volume and increased intraocular pressure? 13:49:21 13:49:22 13:49:25 13:49:28 13:49:32 13:49:35

MS. KAYALI: Objection. Vague. 13:49:38

THE WITNESS: And just ask your question one more time. 13:49:45 13:49:46

BY MS. CHACON: 13:49:47

Q Do you understand the label to be reporting here that the overdoses for the 8 mg dose were due to increased volume and increased intraocular pressure? 13:49:47 13:49:48 13:49:53 13:49:56

A I do not, that's why I needed you to repeat the question. You said, "due to" which is a cause and effect. 13:50:00 13:50:02 13:50:02

And here it says, "Overdosing was 13:50:02

associated with increased injection volume and subsequently increased intraocular pressure." 13:50:04 13:50:05

So I don't know what was the cause of the increased in pressure. I just know that it was associated on this overdose. 13:50:07 13:50:13 13:50:18

Q So when you read "overdosing was associated with increased injection volume and subsequently with increased intraocular pressure," what does that mean to you? 13:50:20 13:50:22 13:50:25 13:50:31

MS. KAYALI: Objection. Vague. 13:50:33

You can answer. 13:50:34

THE WITNESS: We're missing any detailed report of what went on in those isolated cases of overdoses with 8 mg. 13:50:40 13:50:41 13:50:45

So all this means to me is that that overdosing was associated with increased injection volume. 13:50:48 13:50:51 13:50:54

I don't know if that was an increase of 0.1 injection volume, of more than that, and that it was subsequently associated with increased intraocular pressure. 13:50:55 13:50:57 13:51:02 13:51:05

I don't know if that's because the 13:51:07

physician spoke to the patient and said, "Oh, my gosh, I just gave you an overdose" and that raised the patient's blood pressure, which raised their intraocular pressure. 13:51:08 13:51:13 13:51:16 13:51:18

So, again, there's very little information here in this tiny, little section to tell me anything about what that overdosing did in those isolated cases. 13:51:21 13:51:24 13:51:27 13:51:35

BY MS. CHACON: 13:51:36

Q So for increased intraocular pressure, aside from increased injection volume, are there any other common causes of increased intraocular pressure when administering an anti-VEGF drug? 13:51:36 13:51:48 13:51:52 13:51:57

MS. KAYALI: Objection. Vague. Lacks foundation. 13:52:02 13:52:06

THE WITNESS: For example, if that caused increased inflammation, inflammation is then associated with an increase intraocular pressure. So to answer your question, yes, there are other potential causes. 13:52:09 13:52:10 13:52:14 13:52:19 13:52:23

BY MS. CHACON: 13:52:24

Q Is that a known cause for aflibercept? 13:52:24

MS. KAYALI: Objection. 13:52:30

THE WITNESS: Aflibercept has been 13:52:32
associated in rare instances with increasing 13:52:34
inflammation when used at 2~mg and I believe 13:52:37
with 8 mg as well. 13:52:43

BY MS. CHACON: 13:52:45

Q And do you know if aflibercept, in those 13:52:45
rare instances, whether that increased 13:52:49
inflammation is also associated with increased 13:52:51
intraocular pressure? 13:52:55

A I don't know. 13:52:56

(Simultaneous speakers.) 13:52:58

MS. KAYALI: Sorry. Objection. Lacks 13:52:59
foundation. 13:53:00

You can answer. 13:53:00

THE WITNESS: Yeah. I don't know 13:53:02
specifically. I know in general increased 13:53:03
inflammation is associated with increased 13:53:06
intraocular pressure. 13:53:09

BY MS. CHACON: 13:53:11

Q And you said that's for both 2~mg of 13:53:12
aflibercept and 8 mg of aflibercept? Did I 13:53:18

understand you correctly? 13:53:22

A That's correct. And, in fact, with all 13:53:23

anti-VEGF agents that are used to treat these 13:53:26

retinal diseases. 13:53:29

Q I want to point you to paragraph 164 in 13:54:00

your declaration, which is page 86. 13:54:02

A Okay. One moment. 13:54:06

(Phone ringing.) 13:54:07

THE WITNESS: Okay. Thank you. 13:54:07

BY MS. CHACON: 13:54:54

Q And I want to ask you about the last 13:54:55

sentence in this paragraph where you say, 13:55:02

"Therefore, POSA could not have assumed that 13:55:05

quadrupling the dose necessarily resulted in a 13:55:05

quadrupled volume and that any absorbed spikes in 13:55:07

intraocular pressure were solely attributable to 13:55:11

increased volume." 13:55:13

And I'd like to know what your basis is 13:55:15

for that opinion. 13:55:18

MS. KAYALI: Objection. Vague. 13:55:25

THE WITNESS: That opinion is based on 13:55:33

the extremely limited data provided on these 13:55:34

isolated cases. 13:55:38

It's typical to have extensive 13:55:38

paragraphs describing what happens in overdoses 13:55:41

and all the details of follow-up on those cases. 13:55:43

BY MS. CHACON: 13:55:48

Q So, for example, if there was some other 13:55:48

significant safety issue that occurred, would you 13:55:55

expect Regeneron to have to report it to, in this 13:55:57

case, the Australian regulatory body and then 13:56:03

subsequently make its way into the label? 13:56:08

MS. KAYALI: Objection. Calls for 13:56:11

speculation. Incomplete hypothetical. Lacks 13:56:11

foundation. 13:56:13

THE WITNESS: I would expect Regeneron 13:56:16

to report to the authorities all safety concerns 13:56:17

that they had. 13:56:21

BY MS. CHACON: 13:56:22

Q I'm going to mark what I believe should 13:56:22

be a new Exhibit 1077. 13:57:37

(Petitioner's Exhibit 1077 was marked 13:57:40

for identification, the original of which is 13:57:40

attached hereto.) 13:57:40

MS. KAYALI: Sorry. Did you say "new exhibit," Counsel? 13:57:46 13:57:47

MS. CHACON: Correct. 13:57:50

THE WITNESS: Okay. 13:57:51

MS. CHACON: This is a copy of the Australian product information for Lucentis. 13:57:52 13:57:54

MS. KAYALI: Thank you. And before you ask any questions, I'll object to this document under -- because it's not part of the record of this proceeding, under Rule 403 as hearsay under authenticity grounds and on relevance grounds. 13:58:04 13:58:04 13:58:07 13:58:09 13:58:12 13:58:17

And I apologize. Could you, just for my own insanity, repeat the exhibit number you've given? 13:58:26 13:58:29 13:58:33

MS. CHACON: It should be 1077, I believe. 13:58:34 13:58:35

MS. KAYALI: Thanks. 13:58:36

BY MS. CHACON: 13:58:37

Q All right. Dr. Bressler, I've handed you, which is a copy of the Australian product information for Lucentis, Ranibizumab, and I'd 13:58:37 13:58:45 13:58:47

like for you to please turn your attention to page 16 of the document. 13:58:51 13:59:04

A Okay. I'm just going to look through it first so I can put that into context, please. I'm almost done. 13:59:08 13:59:10 14:01:35

Q No problem. Take your time. 14:01:36

A Thank you. 14:01:38

Q And just whenever you're ready, we are going to be on page 16 -- 14:01:38 14:01:40

A Okay. 14:01:42

Q -- Section 4.9. 14:01:43

A Okay. Thank you. And when was this from? 14:03:46 14:03:48

Q This is -- this is a more recent label, so the date of this particular revision is actually from December of last year. 14:03:48 14:03:52 14:03:54

A So after 2018? 14:03:56

Q Correct. 14:03:57

A Got it. 14:03:58

Q Okay. So I'm using this by way of example. So if you go to page 16 in Section 4.9, you'll see there's also an overdosage section in 14:03:59 14:04:02 14:04:07

this Australian Lucentis label. 14:04:10

Do you see that? 14:04:14

A I do. 14:04:14

Q And it reports on cases of accidental overdose that have been reported from clinical studies in wet AMD and post-marketing data. 14:04:15 14:04:17 14:04:18

Do you see that? 14:04:21

A I do. 14:04:22

Q And it goes on to specify particular adverse reactions that were most frequently associated with the reported cases, and that could includes things like "intraocular pressure increased, transient blindness, reduced visual acuity, corneal oedema, corneal pain, and eye pain." 14:04:22 14:04:25 14:04:27 14:04:31 14:04:31 14:04:34 14:04:34

Do you see that? 14:04:41

A I do. 14:04:42

Q Okay. And my question to you is: Is this the additional, I guess, type of detail that you would be looking for, you know, for the aflibercept overdose information in Exhibit 1009? 14:04:43 14:04:47 14:04:51 14:04:56

MS. KAYALI: Objection. Vague. Lacks 14:05:04

foundation. 14:05:06

THE WITNESS: Typically, if I were 14:05:11

evaluating this, I would be looking for much more 14:05:12

information than this. 14:05:15

For example, I'm not even told what the 14:05:17

magnitude of the increased injection volume is. 14:05:18

I'm not told how long afterwards they were 14:05:22

monitored, what the routine was for monitoring 14:05:25

them. 14:05:29

So I would say this is still inadequate 14:05:29

for what I would be looking for to understand 14:05:34

safety of overdosage. 14:05:39

BY MS. CHACON: 14:05:41

Q So they do discuss adverse reactions 14:05:41

that were most frequently associated with the 14:05:44

reported cases. 14:05:45

If there had been similar adverse 14:05:47

reactions for 8 mg of aflibercept, would you have 14:05:50

expected to see that reported in the Australian 14:05:54

label for EYLEA? 14:05:57

MS. KAYALI: Objection. Lacks 14:05:59

foundation. Incomplete hypothetical. Vague. 14:06:00

THE WITNESS: I believe the summary statements would be based on the details of the safety cases that they have, so it's difficult, if not impossible, without that detail for each of the instances to know if the information here would be similar to the information in the Australian label that we were looking at. 14:06:11 14:06:12 14:06:16 14:06:20 14:06:24 14:06:27 14:06:32

BY MS. CHACON: 14:06:35

Q Okay. And I guess my point is, if the Australian label for Lucentis was reporting on other adverse reactions or events that were observed for an overdosage for Lucentis, wouldn't it be fair to assume that if such adverse reactions were observed or existed for 8 mg aflibercept, that those also would have been reported in the label? 14:06:35 14:06:42 14:06:46 14:06:49 14:06:55 14:06:58 14:07:02 14:07:05

MS. KAYALI: Objection. Lacks foundation. Incomplete hypothetical. Vague. 14:07:08 14:07:09

You can answer. 14:07:13

THE WITNESS: And I apologize, but I'll ask you to repeat the question. I was formulating my answer but also listening. 14:07:23 14:07:24 14:07:27

BY MS. CHACON: 14:07:29

Q My point is if the Australian label for 14:07:29

EYLEA -- let me try asking it again. 14:07:31

If the Australian label for Lucentis is 14:07:39

reporting on other adverse reactions that were 14:07:44

associated with and observed for overdoses and 14:07:47

it's reported in an Australian label, wouldn't it 14:07:52

be fair to assume that if such similar types of 14:07:56

adverse reactions were observed for 8 mg overdoses 14:07:59

of aflibercept, that one would expect to see those 14:08:04

in the Australian label for EYLEA if such adverse 14:08:09

reactions existed? 14:08:12

MS. KAYALI: Objection. Incomplete 14:08:14

hypothetical. Vague. And lacks foundation. 14:08:15

Compound. 14:08:20

THE WITNESS: It is hard to compare the 14:08:21

two. First of all, they're across very different 14:08:23

years, so maybe the amount of data that they're 14:08:26

sharing or discussing are different. 14:08:29

And, again, I would really need the 14:08:31

details of these cases to understand if the 14:08:34

descriptions are comparable or not comparable in 14:08:42

one group than the other. 14:08:50

BY MS. CHACON: 14:08:52

Q Okay. Now, in the overdosage section in 14:08:52

Exhibit 1077 that we marked, there is a note at 14:08:56

the bottom that says, "For information on the 14:09:00

management of overdose, contact the poisons 14:09:03

information center on 131126 (Australia.)" 14:09:06

Do you see that? 14:09:12

A I do. 14:09:13

Q And if you -- let's see. There's a 14:09:14

similar statement in Exhibit 1009, which is the 14:09:23

Australian label for EYLEA on page 35. If you can 14:09:30

just open that back up and take a look at that. 14:09:36

A Okay. Thank you. 14:09:52

Q Sure. Now, you agree it's a similar 14:09:53

statement about noting the poison information 14:09:58

center in both of those labels? 14:10:01

A They're not identical. 14:10:06

Q Right, but they mention the poison 14:10:07

information center in both? 14:10:09

A They do. 14:10:14

Q Okay. Do you have any idea, 14:10:15

Dr. Bressler, whether or not that language about consulting the poison information center is standard in an Australian product information label? 14:10:18 14:10:23 14:10:27 14:10:31

A I do not know. 14:10:33

Q Did you look into that in forming your opinions in this case? 14:10:35 14:10:37

A I did not look into it, whether it was standard. I know that it's listed here with the Exhibit 1009. 14:10:40 14:10:42 14:10:49

Q Did you investigate whether or not that language is required for all drug labels in Australia? 14:10:51 14:10:53 14:10:55

A I did not investigate that in order to see if they did require it, why they would require it. 14:10:58 14:11:01 14:11:05

Q Dr. Bressler, you mentioned that you review the anti-VEGF drug labels before you administer it to your patients because you want to make sure that you're precise in how you're administering the dose; is that right? 14:12:07 14:12:09 14:12:16 14:12:18 14:12:20

A That is a reason I've looked at the 14:12:23

labels. 14:12:24

Q Okay. Do you know, Dr. Bressler, 14:12:25

whether for all anti-VEGF treatments, if there's 14:12:27

any sort of standard advisement in the labels to 14:12:34

monitor for increased ocular pressure? 14:12:37

MS. KAYALI: Objection. Lacks 14:12:39

foundation. 14:12:40

THE WITNESS: I'm not aware of what 14:12:42

standard labels have in terms of monitoring 14:12:47

intraocular pressure. 14:12:50

I anticipate that it's been mentioned in 14:12:52

the past, but I would have to go back to look at 14:12:56

the label to see. 14:12:58

BY MS. CHACON: 14:12:59

Q And you referred to several anti-VEGF 14:12:59

drug labels in your declaration; is that right? 14:13:04

A That is correct. 14:13:07

Q And did you look at that issue at all 14:13:07

when you were evaluating those anti-VEGF drug 14:13:10

labels in forming your opinions? 14:13:15

MS. KAYALI: Objection. Vague. 14:13:17

You can answer. 14:13:18

THE WITNESS: I cannot recall specifically looking up in each of the labels what was said about how to monitor intraocular pressure. That's just part of standard care, though. 14:13:22 14:13:23 14:13:27 14:13:31 14:13:33

BY MS. CHACON: 14:13:34

Q Turning back to safety for a moment. I believe in your declaration, Dr. Bressler, that you talk about some of the preclinical toxicity data for aflibercept in forming your opinions. 14:13:34 14:13:40 14:13:43 14:13:50

Do you recall that? 14:13:53

And maybe a different way to ask it, Dr. Bressler, is -- 14:15:00 14:15:03

A I'm almost there. 14:15:04

Q Sure. 14:15:05

A Very good. Okay. So I do recall that. 14:15:14 14:15:15

Q Okay. And one of the exhibits that you refer to is the 2012 EPAR document, which is Exhibit 1058. 14:15:16 14:15:22 14:15:27

Do you recall that? 14:15:28

A I see it's in my materials that I relied 14:15:56

upon, but you'd have to point to me where I mentioned it in the declaration without my having to read the whole declaration. 14:15:59 14:16:05 14:16:07

Q Sure, and I don't want to have to make you do that. I'm going to show it to you here in a second, but I just wanted to get an understanding of, when you considered and relied upon that exhibit, did you review the entirety of the 2012 EPAR? 14:16:10 14:16:11 14:16:13 14:16:14 14:16:17 14:16:20

A If you can point to me where I have it, it would help me remember how much of that I reviewed. 14:16:30 14:16:32 14:16:34

Q Sure. And I can actually give it to you. Why don't we do that? So I'm going to hand you what's already been marked in the proceeding as Alvotech Exhibit 1058. 14:16:35 14:16:36 14:16:42 14:16:43

And that's the European Medicines Agency assessment report, September 20th, 2012. 14:16:49 14:16:52

(Petitioner's Exhibit 1058 was marked for identification, the original of which is attached hereto.) 14:17:05 14:17:05 14:17:05

THE WITNESS: Thank you. 14:17:06

BY MS. CHACON: 14:17:23

Q Now having this in hand, does this 14:17:23

refresh your recollection about the 2012 -- and 14:17:26

I'm calling it EPAR. 14:17:29

I know that's an abbreviation for it, 14:17:30

but the European Medicines Agency assessment 14:17:30

report. 14:17:34

A I do recall looking at this document. 14:17:36

Q Okay. Did you look at this document in 14:17:38

preparation for your deposition today? 14:17:40

A I don't recall looking at this document 14:18:15

in preparation for the deposition today. 14:18:17

Q Going back to my original question, when 14:18:25

you were formulating your opinions in this 14:18:27

proceeding, did you review the entirety of the 14:18:29

European Medicines Agency assessment report? 14:18:32

A So I don't recall what portion of this I 14:18:38

reviewed in preparing my declaration. 14:18:41

Q Would you have looked up any information 14:18:46

in here related to overdoses in clinical trials? 14:18:49

A I would need to look at my declaration 14:18:56

to see where I referenced this to jog my memory. 14:18:57

Q I'd like you to turn to page 64 in this document. And there's a heading at the bottom titled "Overdose." 14:19:05 14:19:15 14:19:33

Let me know when you're there. 14:19:35

A Okay. One minute. Okay. Thank you. 14:19:36

Q Sure. Do you recall reviewing this portion of the 2012 EPAR in formulating your opinions in this case? 14:20:55 14:20:58 14:21:02

A I can't recall, but if you can point to the area in my declaration where I mentioned this exhibit, it might jog my memory. 14:21:05 14:21:07 14:21:10

Q I don't know that you have. That's why I'm asking if you recall, because I don't know if you've specifically mentioned or addressed these overdosages in here. 14:21:14 14:21:15 14:21:18 14:21:22

A No. I do not recall. 14:21:24

Q Okay. All right. So on page 64, under "overdose," it reports, "In clinical studies with VEGF trap-eye isolated cases of overdose of up to tenfold were generally well-tolerated. 14:21:25 14:21:30 14:21:34 14:21:39

"One subject received a single dose of 20 mg VGFT trap-eye in 500 mL volume instead of 14:21:41 14:21:43

the planned 2 mgs and 50 mL volume, which was associated with increased injection volume and subsequently with the transient increase in IOP lasting one day. 14:21:51 14:21:55 14:21:57 14:21:57

"No other TEAE were observed. As of January 2011, all overdosed subjects recovered without sequelae." 14:22:00 14:22:04 14:22:08

So looking at that, Dr. Bressler, does that provide you with any further information about potential or observed adverse events with overdoses of aflibercept? 14:22:13 14:22:19 14:22:24 14:22:31

MS. KAYALI: Objection. Vague. 14:22:34

You can answer. 14:22:41

THE WITNESS: Unfortunately, it's still extremely limited. For example, it says "isolated cases." So I don't know if that's 2, 3, 12 -- more. It says "up to tenfold." 14:22:45 14:22:46 14:22:51 14:22:56

I don't know if one of them was tenfold and the others were onefold. It says they were generally well-tolerated, which doesn't mean it was safe completely. 14:22:58 14:23:00 14:23:02 14:23:05

It talks about one subject receiving 14:23:07

this single dose. And without any sort of additional detail, it fails to tell me what I would need and what I think a POSA would need to understand what overdoses could do if given -- if those were given to individuals. 14:23:10 14:23:14 14:23:18 14:23:25 14:23:28

BY MS. CHACON: 14:23:29

Q Okay. It does provide detail of at least one subject that received a single dose of 20 mgs and 500 mL; correct? 14:23:29 14:23:34 14:23:36

A It does give detail of a sentence or two sentence -- a sentence of that one subject receiving that single dose. Correct. 14:23:42 14:23:46 14:23:50

Q And as far as any safety concerns with it, those two sentences are reporting that "that patient had a transient increase in IOP lasting one day but that no other TAAEs [sic] were observed"; is that right? 14:23:52 14:23:55 14:23:59 14:24:02 14:24:06

A It does say that for one patient. 14:24:08

Q One patient who received 10 times the amount of 2~mg of EYLEA; correct? 14:24:12 14:24:14

A It does describe that for one patient. Correct. 14:24:19 14:24:21

Q Okay. And so understanding that there were no other observed TEAEs and apart from that, the only other observation was a transient increase in IOP lasting one day, wouldn't that suggest to a POSA that overdosages of EYLEA don't present significant adverse facts? 14:24:26 14:24:28 14:24:33 14:24:37 14:24:40 14:24:48

A I don't -- 14:24:54

MS. KAYALI: Objection. Lacks foundation. 14:24:55 14:24:56

You can answer. 14:24:56

THE WITNESS: I don't think it suggests that at all, because it's just one subject. What if the next nine subjects had terrible adverse events with that. 14:24:57 14:24:58 14:25:01 14:25:05

So I -- I know that a POSA would not be comfortable with safety information here regarding overdosage when being told of one or two or even a few patients that may have gotten to that level of overdose. It's just not sufficient to understand the safety. 14:25:05 14:25:11 14:25:15 14:25:22 14:25:26 14:25:29

BY MS. CHACON: 14:25:31

Q So this is Regeneron providing data to 14:25:31

the European Medicines Agency; correct? 14:25:34

MS. KAYALI: Objection. Lacks 14:25:42

foundation. 14:25:43

THE WITNESS: Correct. This is 14:25:52

Regeneron presenting that. To the best of my 14:25:53

knowledge, I don't know if perhaps buyer presented 14:25:57

it instead, so -- 14:26:00

BY MS. CHACON: 14:26:02

Q Sure. 14:26:02

A -- I'm not sure. 14:26:03

Q Okay, but if there had been for these 14:26:04

other instances -- isolated cases of overdose up 14:26:07

to tenfold -- if there had been other TEAEs or 14:26:11

other observations of transient increases in IOP, 14:26:17

wouldn't those be reported here? 14:26:23

MS. KAYALI: Objection. Calls for 14:26:25

speculation. Lacks foundation. 14:26:26

You can answer. 14:26:30

THE WITNESS: I don't know what would be 14:26:32

reported, but even if there were additional 14:26:33

details, the interpretation of isolated cases is 14:26:35

too few to know if it's safe at all and, again, I 14:26:40

don't know what would have to be reported given what happens with the overdosage. 14:26:45 14:26:49

BY MS. CHACON: 14:26:51

Q Do you know whether it's possible if Regeneron could hold back that the kind of information from the European Medicines Agency? 14:26:51 14:26:54 14:26:56

MS. KAYALI: Objection. Lacks foundation. 14:27:03 14:27:04

You can answer. 14:27:04

THE WITNESS: It's my expectation that they would not hold back that information, but that also doesn't tell me if they received all that information. 14:27:05 14:27:08 14:27:11 14:27:14

BY MS. CHACON: 14:27:19

Q You mean Regeneron received that information or the European Medicines Agency? Who is the "they"? 14:27:19 14:27:21 14:27:24

A The "they" is the -- Regeneron. 14:27:26

Q So you don't know whether Regeneron received all of the information regarding the isolated cases of overdoses that are reported here? 14:27:28 14:27:30 14:27:33 14:27:36

A I don't know. It's not listed there. 14:27:38
So they may have requested some additional 14:27:39
information, it wasn't available, and that's how 14:27:43
they reported it to the agency, that that 14:27:47
additional information wasn't available. 14:27:50
I cannot tell from the two-sentence 14:27:52
description that's given here -- 14:27:55
Q Okay. 14:27:57
A -- in those isolated cases. 14:27:57
Q Is that typical, where an innovator is 14:28:01
not given information about -- information from 14:28:06
they're clinical studies? 14:28:12
MS. KAYALI: Objection. Lacks 14:28:13
foundation. Calls for speculation. 14:28:15
You can answer. 14:28:19
THE WITNESS: In the clinical trial 14:28:25
where the protocols are followed, I think it's 14:28:27
typical that they have the information that they 14:28:30
think they need. 14:28:32
Where there's an exceptional 14:28:33
circumstance, such as isolated case of overdose, I 14:28:35
cannot speculate as to whether it's typical that 14:28:41

they get all the information that they need or they don't, because it's such unusual circumstances. 14:28:45 14:28:47 14:28:49

BY MS. CHACON: 14:28:50

Q So even though these isolated cases of overdoses were observed in clinical studies with VEGF trap-eye, you couldn't say one way or another whether or not Regeneron would have access to the data? 14:28:50 14:29:01 14:29:04 14:29:10 14:29:12

MS. KAYALI: Objection. Asked and answered. 14:29:16 14:29:17

THE WITNESS: They would have access to the data. I don't know if they would have all the data they need to tell a POSA in these isolated cases which, again, are concerning just by the inferred few number of cases, whether the overdoses were safe. 14:29:21 14:29:22 14:29:24 14:29:29 14:29:32 14:29:35

BY MS. CHACON: 14:29:42

Q Did you ask to speak with anyone at Regeneron about that in forming your opinions in this case? 14:29:42 14:29:46 14:29:50

A I did not speak with anyone with 14:29:52

Regeneron in forming my opinions for this case. 14:29:54

Q Could you have? 14:29:58

A I don't know. I would have to ask 14:30:05

counsel if I can discuss that with Regeneron. 14:30:07

That might be a legal question from my 14:30:09

perspective. 14:30:13

Q And just another question on this 14:30:42

briefly, Dr. Bressler. So the last sentence on -- 14:30:43

in the overdosage section -- I'm sorry -- of that 14:30:46

paragraph that we were looking at says -- 14:30:49

MS. KAYALI: Which exhibit are you in? 14:30:53

I apologize for interrupting. 14:30:54

MS. CHACON: Same one. 1058. 14:30:55

MS. KAYALI: Okay. 14:30:57

BY MS. CHACON: 14:30:57

Q So, Dr. Bressler, in that first 14:30:57

paragraph under "overdosage," the last sentence 14:31:01

says, "As of January 2011, all overdose subjects 14:31:04

recovered without sequelae." 14:31:09

What does "recovered without sequelae" 14:31:12

mean? 14:31:19

A It implies to me that there were no 14:31:29

long-term safety issues for as long as they followed these individuals which, again, I don't know how long they followed them. 14:31:34 14:31:43 14:31:45

Q So "recovered without sequelae" means that they recovered without any long-term safety issues? 14:31:49 14:31:57 14:32:00

Did I understand you correctly? 14:32:00

MS. KAYALI: Objection. Lacks foundation. 14:32:02 14:32:03

You can answer. 14:32:09

THE WITNESS: Number one, I said that's what it implies to me, that they didn't have any longer term safety issues. 14:32:10 14:32:12 14:32:15

But, again, I don't even know how long those individuals were followed for such safety problems. 14:32:16 14:32:19 14:32:23

MS. KAYALI: And, Counsel, if we're going to move to a new exhibit, can we take a quick five-minute break? 14:32:36 14:32:37 14:32:40

THE WITNESS: I'm going to vote yes and not have a long question since that -- 14:32:43 14:32:44

MS. CHACON: Yes, we can do that. 14:32:47

THE WITNESS: That would be preferrable. 14:32:49
MS. CHACON: Let's go off the record. 14:32:50
THE VIDEOGRAPHER: We are going off the 14:32:51
record. The time is 14:32. 14:32:52
(Recess.) 14:32:57
THE VIDEOGRAPHER: We are going back on 14:53:39
the record. The time is 14:53. 14:53:41
BY MS. CHACON: 14:53:45
Q Dr. Bressler, all day today we've been 14:53:45
talking about your declaration, which is in 14:53:48
response to Dr. Don D'Amico. 14:53:50
Do you know Dr. D'Amico? 14:53:53
A I do. 14:53:56
Q How do you know Dr. D'Amico? 14:53:56
A He's a colleague in retina. He was on 14:53:59
faculty when I was doing my residency and 14:54:03
fellowship at Mass Eye & Ear in 1983 through 1986, 14:54:05
and we have collaborated at meetings and studies 14:54:11
over the next 40 years. 14:54:17
Q When you say that he was on faculty 14:54:20
while you were during your residency and 14:54:23
fellowship, does that mean that he was your -- for 14:54:25

lack of a better word, he was one of your teachers? 14:54:28 14:54:31

MS. KAYALI: Objection. Foundation. 14:54:32

You can answer. 14:54:33

THE WITNESS: He was an early career faculty member who would teach what he knew about retina to the residents, including myself. 14:54:38 14:54:40 14:54:48

BY MS. CHACON: 14:54:52

Q And what are your thoughts about Dr. D'Amico? 14:54:52 14:55:01

MS. KAYALI: Objection. Vague. 14:55:02

THE WITNESS: In general, he is a thoughtful administrator as a Chair, recently retired at Weill Cornell, and he has extensive surgical experience and is very good at teaching people about that surgery in retina. 14:55:08 14:55:15 14:55:21 14:55:30 14:55:33

BY MS. CHACON: 14:55:37

Q Do you believe him to be an expert in intravitreal injection for anti-VEGF drugs? 14:55:37 14:55:40

A I'm not sure what an expert in intravitreal anti-VEGF drugs means. I know that he treats people with intravitreal anti-VEGF 14:55:51 14:55:53 14:55:57

drugs, and he has participated in studies that have involved intravitreal anti-VEGF drugs. It's not the focus of his research to design or oversee those trials. 14:56:02 14:56:06 14:56:13 14:56:17

Q Do you believe Dr. D'Amico is a good clinician? 14:56:23 14:56:31

A I do believe Dr. D'Amico is a good clinician. 14:56:32 14:56:34

Q And you said over the course of 40 years, that you've collaborated with him? 14:56:39 14:56:40

A Correct. 14:56:43

Q In what context have you collaborated with him? 14:56:44 14:56:47

A For example, when I was Chair of National Eye Institute multicenter trial called the submacular surgery trials, he was at Massachusetts Eye & Ear infirmary and was one of the clinical site investigators for that trial, as we would have multiple sites around the country participate in that trial that I chaired. 14:56:48 14:56:48 14:56:48 14:56:55 14:56:58 14:57:01 14:57:04

For another example, we've had numerous continuing medical education courses where either 14:57:08 14:57:11

he invited me to speak or I invited him to speak. 14:57:15

Q I also wanted to ask you about your 14:57:32

familiarity with Regeneron. We've talked a lot 14:57:37

about Regeneron today. 14:57:41

Have you ever worked with Regeneron, and 14:57:43

when I say that, I mean in a nonlegal capacity. 14:57:49

MS. KAYALI: Objection. Vague. 14:57:55

You can answer. 14:57:56

THE WITNESS: My university has done 14:58:03

clinical research with Regeneron in which I've 14:58:04

been an investigator and has done institutional 14:58:12

service agreements where I provided expertise in 14:58:20

clinical trial design to discuss designing and 14:58:22

implementing clinical trials that they've worked 14:58:27

on in retinal diseases. 14:58:31

BY MS. CHACON: 14:58:34

Q Are you on any speaking boards or key 14:58:34

opinion leaderboards for Regeneron? 14:58:39

A I am not. Our university precludes that 14:58:42

participation. 14:58:48

Q So your university precludes 14:59:01

participation on speaker boards or key opinion 14:59:03

leaderboards, but they are okay with participation in legal proceedings? 14:59:06 14:59:09

A They are okay with participation in legal proceedings. 14:59:12 14:59:15

Q Do you have any personal interest in Regeneron; stocks, other investments, things of that nature? 14:59:21 14:59:25 14:59:29

A None. 14:59:30

Q I think I heard you say earlier, Dr. Bressler -- and again, without getting into confidential third party, but that you were working with a biosimilar manufacturer; is that correct? 14:59:34 14:59:37 14:59:41 14:59:43 14:59:47

A I was. 14:59:48

Q All right. And do you utilize biosimilars in your clinical practice at all? 14:59:48 14:59:55

A I do when it's required by the patient's insurance or otherwise they would not have access to getting treated. 15:00:00 15:00:04 15:00:08

Q Do you believe biosimilars offer a benefit to patients in the U.S., the availability of them? 15:00:12 15:00:15 15:00:22

MS. KAYALI: Objection. Vague. Lacks foundation. Outside the scope. 15:00:22 15:00:30

THE WITNESS: While, I wasn't asked to consider biosimilars, to answer your question, the benefit could be access where an insurance company or otherwise would not allow someone to get them and could reduce the costs, and I emphasize "could" because it doesn't always work that way in the marketplace. 15:00:34 15:00:36 15:00:42 15:00:45 15:00:48 15:00:53 15:00:56

BY MS. CHACON: 15:01:03

Q Are you currently collaborating with any biosimilar manufacturers? 15:01:03 15:01:05

A I am not. 15:01:15

Q Let's turn back to -- and if you could, please, turn to paragraph 53 in your declaration for me. 15:01:27 15:01:33 15:01:35

A And what section is that in? 15:01:39

Q That would be -- it's on -- the section starts on page 27, paragraph 53 is on page 28, and I believe that is Section 7A. 15:01:43 15:01:47 15:01:51

A 7A, page 27? Okay. Just one minute, please. 15:02:04 15:02:07

Q Sure. 15:02:07

A Okay. Thank you. I'm -- I'm ready. 15:03:06

Q All right. So in -- let's start with 15:03:09
Section A that you just reviewed. So does this 15:03:12
provide some background on VEGF and aflibercept; 15:03:16
is that correct? 15:03:21

A It does. 15:03:21

Q Now, aflibercept is a recombinant fusion 15:03:24
protein. I believe you discussed that in 15:03:30
paragraph 53; is that right? 15:03:32

A Correct. 15:03:38

Q And, Dr. Bressler, are you aware of any 15:03:40
other recombinant fusion proteins that are used 15:03:42
for treating angiogenic eye disorders? 15:03:48

A I would have to go back to look at it, 15:03:54
because the basic science information is something 15:03:56
I have a general understanding for but not detail. 15:03:59

And so, I believe, but I'm not positive 15:04:02
unless I looked it up, that arisaema may also 15:04:05
include a recombinant fusion protein, but I'm not 15:04:09
certain. 15:04:13

Q Okay. And when you say "the basic 15:04:14

science information," are you referring to things like the difference between a recombinant fusion protein versus a monoclonal antibody versus a small molecule -- I want to make sure I understand what you mean by "basic science." 15:04:16 15:04:18 15:04:20 15:04:24 15:04:26

A All of those. The Fc portion of human IgG1. 15:04:29 15:04:30

Q I'd like to get a better understanding from you, Dr. Bressler, in terms of how aflibercept works. So we talked earlier about your injection procedures and getting aflibercept into the eye. 15:04:41 15:04:43 15:04:48 15:04:51 15:04:54

Once the aflibercept is in the eye, what is it doing? 15:04:55 15:04:59

MS. KAYALI: Objection. Vague. 15:05:01

You can answer. 15:05:02

THE WITNESS: So, again, from my basic science perspective, I could only answer very simply what it's doing, which I'll do in the next sentence or two. 15:05:08 15:05:10 15:05:13 15:05:15

From a clinical trial perspective, I know that when it's used, it works in terms of 15:05:15 15:05:18

improving visual acuity outcomes compared with not using it. 15:05:22 15:05:23

But, again, what it's doing, I can't tell you. I've been told that it goes from the vitreous to penetrate into the retina and bind or mop up VEGF that was contributing to or causing various retinal diseases like the neovascular form of macular degeneration or diabetic macular oedema, but that's a very superficial explanation. 15:05:24 15:05:26 15:05:28 15:05:33 15:05:38 15:05:42 15:05:47

BY MS. CHACON: 15:05:50

Q Do you have an understanding of how specifically aflibercept binds to VEGF in the eye? 15:05:51 15:05:54

MS. KAYALI: Objection. Lacks foundation. Vague. 15:06:01 15:06:02

You can answer. 15:06:03

THE WITNESS: Again, this is not my area of detail to understand. For example, in paragraph 53, I said, "Aflibercept binds VEGF-A and placental growth factor, or PlGF dimers in a 1:1 ratio, a mechanism is described as a powerful two-fisted grasp." 15:06:08 15:06:10 15:06:13 15:06:17 15:06:21 15:06:26

And that is what I have heard from 15:06:27

experts in the field, that I have every reason to believe who are an expert in giving the appropriate information and explanation of something like that, but that would be the extent of my understanding of how they bind. 15:06:31 15:06:33 15:06:36 15:06:38 15:06:40

BY MS. CHACON: 15:06:42

Q So in your career, have you ever studied the differences and sort of the mechanism of action between aflibercept versus other anti-VEGF drugs that are out there; bevacizumab, ranibizumab, any of the more recent drugs? 15:06:42 15:06:50 15:06:54 15:06:59 15:06:59

MS. KAYALI: Objection. Lacks foundation. Vague. 15:07:06 15:07:07

You can answer. 15:07:10

THE WITNESS: I haven't studied the basic science mechanisms of action. I've studied in clinical trials how retinal diseases respond to one agent versus another. 15:07:14 15:07:17 15:07:20 15:07:26

BY MS. CHACON: 15:07:28

Q Is that something a clinician would typically do, or is that more in sort of the research scientist lane? I'm just trying to 15:07:28 15:07:42 15:07:45

understand who -- who is the type of person who studies that? 15:07:48 15:07:50

MS. KAYALI: Objection. Lacks foundation. Vague. 15:07:51 15:07:56

You can answer. 15:07:57

THE WITNESS: A person who does laboratory research, which could be a physician or it could be someone who only does laboratory research and is not a physician. 15:08:01 15:08:02 15:08:05 15:08:08

BY MS. CHACON: 15:08:10

Q And do you think it's important in understanding the differences of how aflibercept works to bind VEGF as compared to other anti-VEGF drugs to make comparisons between the two? 15:08:11 15:08:12 15:08:15 15:08:26

MS. KAYALI: Objection. Lacks foundation. Vague. 15:08:30 15:08:31

THE WITNESS: Could you repeat the question? 15:08:44 15:08:45

BY MS. CHACON: 15:08:45

Q Do you think it's important to understand the differences of how aflibercept binds to VEGF as compared to other anti-VEGF drugs 15:08:45 15:08:47 15:08:50

in order to make comparisons between the two? 15:08:55

MS. KAYALI: Objection. Lacks 15:08:58

foundation. Vague. 15:08:59

THE WITNESS: I think it's important at 15:09:01

the stage of hypothesizing if something is worth 15:09:01

pursuing further within a clinical trial. 15:09:06

Having a basic science mechanism that is 15:09:09

explained by experts in the laboratory that sounds 15:09:11

like it makes rational sense is important, but it 15:09:15

doesn't determine whether you would have 15:09:19

improvement with those agents until you actually 15:09:22

test it. 15:09:25

There are a myriad of ideas that have 15:09:26

been shown to be beneficial in the laboratory 15:09:29

that, when subjected to clinical trials, are not 15:09:31

found to bear what was suspected. So I hope that 15:09:34

summarizes the importance I placed on it. 15:09:40

BY MS. CHACON: 15:09:43

Q Now, you note that, in paragraph 53, 15:09:43

that "Aflibercept functions as a soluble decoy 15:10:09

receptor that binds to VEGF-A, VEGF-B, VEGF-C and 15:10:14

PlGF with higher affinity than their natural 15:10:19

receptors." 15:10:24

Do you see that? 15:10:26

A I do. 15:10:27

Q So what does that mean? 15:10:27

A To me, as a clinician and not an expert in basic science of this information, it means that this is a way that it mops up the ability of VEGF to cause neovascular AMD, for example, or diabetic macular oedema. 15:10:34 15:10:37 15:10:41 15:10:48 15:10:57

Q And in the next paragraph, paragraph 54, you contrast aflibercept to other anti-VEGF agents, particularly bevacizumab and ranibizumab, which target only VEGF-A isoforms. 15:11:02 15:11:04 15:11:12 15:11:14

Do you see that? 15:11:19

A I do see that. 15:11:20

Q And why are you comparing or contrasting aflibercept to those to anti-VEGF drugs? 15:11:21 15:11:23

A To explain the state of the art, those are the three agents that were being used at the time, and I'm sharing what is known about how they theoretically may differ so that they theoretically may cause different clinical trial 15:11:33 15:11:37 15:11:40 15:11:46 15:11:50

effects and clinical effects once used in a patient. And so these are what we're known to, theoretically, separate out one agent from another. 15:11:53 15:11:57 15:12:00 15:12:03

Q Does the fact that aflibercept binds to VEGF-A with greater affinity than bevacizumab or ranibizumab tell you anything as a clinician? 15:12:13 15:12:16 15:12:20

MS. KAYALI: Objection. Vague. 15:12:23

THE WITNESS: It tells me that the basic scientists have a reason to believe that these may act differently -- and so that adds some biologic rational to see if that results in similar, worse, or better outcomes when using anti-VEGF agents. 15:12:30 15:12:32 15:12:35 15:12:41 15:12:45

BY MS. CHACON: 15:12:50

Q In your experience, do you believe that aflibercept offers any unique properties as an anti-VEGF drug as compared to any other drugs in the class? 15:12:50 15:13:14 15:13:20 15:13:24

MS. KAYALI: Objection. Vague. 15:13:25

You can answer. 15:13:27

THE WITNESS: In my experience from clinical trial results, aflibercept can be 15:13:33 15:13:33

superior to either ranibizumab or bevacizumab when treating the VEGF-driven process of diabetic macular oedema. 15:13:39 15:13:46 15:13:50

BY MS. CHACON: 15:13:52

Q And what about in comparison to some of the more recent anti-VEGF drugs that have been approved, like the Vabysmo and Beovu? 15:13:52 15:13:55 15:13:59

A In my opinion, my interpretation of trials that have gone head-to-head comparing aflibercept 2~mg to Vabysmo or to brolucizumab (Beovu), have not shown any superior outcomes with those agents for visual acuity than with aflibercept 2~mg. 15:14:12 15:14:18 15:14:25 15:14:27 15:14:35 15:14:39

Q Would you agree that aflibercept is better characterized than some of the other recent anti-VEGF drugs that have been approved? 15:14:59 15:15:02 15:15:06

MS. KAYALI: Objection. Vague. 15:15:10

THE WITNESS: I have no idea what "better characterized" means. 15:15:15 15:15:16

BY MS. CHACON: 15:15:19

Q By nature of the fact that aflibercept has been available on the market since 2011. 15:15:19 15:15:22

There's more years of data. More efficacy data, more safety data. 15:15:24 15:15:27

Would you agree that it's better characterized than some of the more recently approved anti-VEGF drugs? 15:15:28 15:15:30 15:15:33

A So I would agree that there is greater clinical trial data with aflibercept 2 mg than the more recently approved faricimab (Vabysmo), brolucizumab (Beovu). 15:15:36 15:15:40 15:15:49 15:15:51

Q Now, if you were looking at -- from the perspective of a person of skill in the art whether there was any motivation to make new or different doses of aflibercept, would you be looking to information from other anti-VEGF drugs? 15:16:08 15:16:10 15:16:15 15:16:19 15:16:24

MS. KAYALI: Objection. Calls for a legal conclusion. Vague. 15:16:31 15:16:34

THE WITNESS: With respect to motivation, I'm not an expert in the law, and the legal standards that I applied were explained in paragraph 28. 15:17:07 15:17:07 15:17:11 15:17:14

BY MS. CHACON: 15:17:19

Q But you provide opinions on what a POSA 15:17:19

would or would not have been motivated to do in your declaration; is that right? 15:17:27 15:17:30

A That is correct. 15:17:32

Q Okay. So what is, then, your understanding of motivation, then, such that you're able to provide those opinions in your declaration? 15:17:32 15:17:35 15:17:38 15:17:40

A And so -- could you just repeat the question now, please? 15:18:05 15:18:07

Q What is your understanding of motivation such that you're able to provide opinions in your declaration about motivation? 15:18:09 15:18:11 15:18:14

A My understanding is that the POSA would not have been motivated to administer 8 mg dose of aflibercept to treat angiogenic eye disorders with a reasonable expectation of success. 15:18:30 15:18:33 15:18:37 15:18:42

Q Okay. And I'm just trying to understand what the POSA would be looking at. 15:18:44 15:18:46

So we've been talking about, sort of the uniqueness of aflibercept as compared to other agents, and I'm trying to understand from your perspective, as a clinician and a POSA, would the 15:18:49 15:18:51 15:18:53 15:18:55

person of skill in the art just be looking at aflibercept art, or would they be looking at art related to other anti-VEGF treatments? 15:19:00 15:19:04 15:19:04

MS. KAYALI: Objection. Incomplete hypothetical. 15:19:09 15:19:11

THE WITNESS: One thing they would be looking at is whether there was evidence to suggest that there's anything out there to increase efficacy in terms of visual acuity outcomes or durability of agents. 15:19:17 15:19:18 15:19:25 15:19:28 15:19:32

BY MS. CHACON: 15:19:45

Q So I'm not sure that answers my question. Does that mean they would be looking at other drugs aside from aflibercept? 15:19:45 15:19:47 15:19:49

MS. KAYALI: Objection. Incomplete hypothetical. 15:19:51 15:19:52

THE WITNESS: They might look at other drugs to see if there's evidence that they may provide, in some way, greater efficacy in terms of visual acuity outcomes or greater duration. 15:20:03 15:20:05 15:20:07 15:20:11

BY MS. CHACON: 15:20:17

Q Now, why is it that you believe that 15:20:17

they would be looking for greater efficacy and greater duration? 15:20:23 15:20:26

A The visual acuity outcomes are most important to the patient who has these diseases, so there would always be a motivation to try to improve on that. 15:20:33 15:20:36 15:20:38 15:20:43

The burden of having to treat monthly or every other month can be challenging, and any opportunities to be able to extend that without -- that duration without sacrificing the visual acuity would motivation someone as well. 15:20:46 15:20:49 15:20:56 15:21:01 15:21:02

Q I want to point you to -- let's see. We're going to fast forward now through your declaration to page 57, Section 3 where you talk about the CLEAR-IT 2 trial, and I believe that's in your Section 7E3 that begins on page 57. 15:21:15 15:21:24 15:21:29 15:21:31 15:21:37

A Thank you. One moment. 15:21:44

Q And I take it, Doctor, you're reading through your Section 3? 15:24:13 15:24:15

A I am just so I can put that paper into context with your question. 15:24:16 15:24:19

Q Sure. No problem. I just wanted to 15:24:21

make sure you weren't waiting for me. 15:24:23

A No, no. Thank you. I'm almost done. 15:24:25

Okay. Thank you so much. 15:25:40

Q Sure. All right. So Section 3 in your declaration starting on page 57 is where you provide your opinions about the CLEAR-IT 2 trial; is that right? 15:25:42 15:25:44 15:25:47 15:25:53

A That is correct. 15:25:53

Q Okay. Now, you've summarized the CLEAR-IT 2 trial in here, but I just want to ask you a few clarifying questions here. 15:25:54 15:25:58 15:26:00

So paragraph 114, you mention -- so second sentence, "Central retinal/lesion thickness or CRLT" -- we haven't really talked about that much today. 15:26:03 15:26:12 15:26:18 15:26:21

Can you explain to me what that is? 15:26:22

A On OCT, Optical Coherence Tomography, you can measure the thickness of the retina and VEGF retinal diseases such as neovascular AMD or diabetic macular oedema can result in varying amounts of leakage of vessels that can cause the retina tissue to thicken like a sponge filling up 15:26:24 15:26:27 15:26:35 15:26:45 15:26:49 15:26:55

with water.

That is then measured on optical coherence tomography and the measurement is divided into a central subfield and four additional pericentral subfields and four additional outer subfields all within the macula of the retina, and the changes in the central subfield are most likely associated with the visual acuity because that is where the cells are to be able to read the eye chart or read -- or have fine central vision.

However, the correlation is not even close to 1:1. And so this is used as a surrogate to determine if there's VEGF activity.

It is used as a surrogate in earlier phase trials to say, "Might I have a beneficial anti-VEGF agent that is not used as a primary outcome to determine, do I have an agent that benefits the patient with these retinal diseases?"

Q Okay. So just so I understand, Central Retinal/Lesion Thickness is a measure of efficacy or perhaps slightly different surrogate for a

measure of efficacy? 15:28:54
Did I understand that correctly? 15:28:56
MS. KAYALI: Objection. 15:28:58
Mischaracterizes testimony. Lacks foundation. 15:28:58
You can answer. 15:29:00
THE WITNESS: No. It's not a surrogate 15:29:01
for efficacy. It's a surrogate to say that an 15:29:02
agent is having an anti-VEGF effect since the VEGF 15:29:05
effect is causing the retina to thicken. 15:29:12
BY MS. CHACON: 15:29:15
Q Okay. So it is a measure of efficacy? 15:29:15
A It is not a measure of visual function 15:29:19
efficacy; it's a measure of an anatomic outcome. 15:29:22
Q How important is it to understand the 15:29:31
impact of an anti-VEGF on anatomic function? 15:29:36
MS. KAYALI: Objection. Vague. 15:29:37
THE WITNESS: I can't tell you how 15:29:39
important it is. I can tell you that it gives us 15:29:39
greater confidence that an agent is working when 15:29:42
visual acuity outcomes are found to be superior 15:29:45
with one agent, then another, and then the OCT 15:29:49
central subfield thickness is bound to be better. 15:29:56

But we have numerous examples in the medical literature where, for example, the central subfield thickness does not improve as well with one anti-VEGF agent, then another, and yet the visual acuity outcomes are indistinguishable. 15:29:59 15:30:02 15:30:06 15:30:10 15:30:17

BY MS. CHACON: 15:30:20

Q Would decreasing CR/LT be considered treatment of an angiogenic eye disorder? 15:30:20 15:30:26

MS. KAYALI: Objection. Excuse me. Vague. Calls for a legal conclusion. 15:30:32 15:30:35

THE WITNESS: Please repeat the question. 15:30:40 15:30:41

BY MS. CHACON: 15:30:42

Q Would decreasing the CR/LT be considered treatment of an angiogenic eye disorder? 15:30:42 15:30:47

MS. KAYALI: Objection. Vague. And calls for a legal conclusion. 15:30:52 15:30:53

THE WITNESS: I don't know what you mean by "treatment." 15:30:54 15:30:55

BY MS. CHACON: 15:30:56

Q Let me say that -- would it be considered shown as an effective treatment for 15:30:56 15:30:59

angiogenic eye disorder? 15:31:04

A No. It would show an atomic outcome 15:31:10

that potentially may indicate something is a 15:31:15

worthwhile agent to pursue going forward for 15:31:23

visual acuity outcomes. 15:31:27

And, again, it's used to inform during 15:31:28

follow-up of treatment whether there's VEGF 15:31:33

activity returning that would warrant resuming 15:31:36

anti-VEGF. 15:31:42

Q Okay. Let me ask it slightly 15:31:45

differently. 15:31:49

Is reducing central retinal thickness, 15:31:51

is that considered treating an angiogenic eye 15:31:54

disorder? 15:32:00

MS. KAYALI: Objection. Asked and 15:32:01

answered. 15:32:01

THE WITNESS: Reducing central retinal 15:32:05

thickness is an effect that is seen with anti-VEGF 15:32:07

agents when the thickness was driven by VEGF. 15:32:14

BY MS. CHACON: 15:32:17

Q Now, CRLT in the CLEAR-IT 2 trial was 15:32:17

the primary objective; primary point; is that 15:32:29

right? 15:32:33

A I'd have to look at the paper again to see if it says in the methods that that was the primary outcome. 15:32:33 15:32:35 15:32:37

That very well could be, I just would need to look at it to see is that the primary outcome for that trial. 15:32:38 15:32:40 15:32:45

Q So let's do that. Let's introduce what has previously been marked as Regeneron Exhibit 2118, the 2011 paper, CLEAR-IT 2. 15:32:48 15:32:51 15:32:54

A Thank you. 15:33:00

(Petitioner's Exhibit 2118 was marked for identification, the original of which is attached hereto.) 15:33:01 15:33:01 15:33:01

BY MS. CHACON: 15:33:23

Q And to verify what we were just discussing, Dr. Bressler, I'd point your attention to page 1099 of the paper under "study design." 15:33:23 15:33:26 15:33:29

A So this clarifies that the primary outcome, which I'm assuming is what they mean when they say the primary objective, was both to assess the effect on the central subfield thickness, 15:33:46 15:33:48 15:33:51 15:33:53

let's say, the CRLT, and to assess the ocular and systemic safety and tolerability of repeated doses. 15:33:59 15:34:03 15:34:06

Q Right. And a -- it notes the secondary objective was to look at the effect on BCVA; is that right? 15:34:07 15:34:10 15:34:15

A That is correct. 15:34:15

Q All right. Now, you, in your declaration, have included discussion of the results from the CLEAR-IT 2 trial. 15:34:22 15:34:24 15:34:27

And in paragraph 115, you note at week 12, "All dosing groups showed a statistically significant mean improvement in visual acuity compared with baseline visual acuity as measured by the best corrected visual acuity letter score on an ETDRS chart;" is that correct? 15:34:31 15:34:40 15:34:44 15:34:46 15:34:50 15:34:51

A That is correct. 15:34:56

Q Okay. So said another way, all of the dosing groups that were in this study showed an improvement in the CBA scores; right? 15:34:57 15:35:00 15:35:04

A Say that again, please. I'm sorry. 15:35:09

Q All the dosing groups that were in this 15:35:11

study showed an improvement in the CBBA [sic] scores? 15:35:13 15:35:17

A The groups showed a statistically significant improvement on average. 15:35:18 15:35:20

Q So I want to point your attention now to -- starting at paragraph 121 where you're discussing rejection outcomes, and you've included in your declaration, Table 4 from 2011, which is Exhibit 2118 that we just looked at. 15:35:34 15:35:37 15:35:42 15:35:46 15:35:53

Do you see where I'm pointing you to? 15:35:56

A I do. 15:35:59

Q Okay. Why did you include Table 4 in the discussion of Table 4 in your declaration? 15:35:59 15:36:06

A I included the table because I thought it was an excellent example without getting lost in text to show how there's inconsistency across increasing doses with its effect on the main number of days to first injection during the PRN phase. 15:36:13 15:36:16 15:36:18 15:36:28 15:36:33 15:36:38

Q Okay. And in paragraph 124 in your declaration, you state, "Likewise, the POSA considering whether to pursue a high dose of 15:36:40 15:36:43 15:36:48

aflibercept product would have compared the PRN phase results of study participants in the 4 mg quarterly arm to the 2 mg monthly arm." 15:36:50 15:36:53 15:36:54

Do you see that? 15:37:01

A I do. 15:37:02

Q Why do you opine that a POSA considering whether to pursue a high dose of aflibercept product would have compared those two arms? 15:37:03 15:37:06 15:37:08

A Because, during the PRN phase, both of those groups had an opportunity to be dosed as frequently as was desired by the protocol, and so it gives an opportunity to compare head-to-head, a PRN phase of giving either 4 mg or 2~mg during that -- during that PRN phase. 15:37:14 15:37:17 15:37:20 15:37:25 15:37:31 15:37:37

And that allows the POSA to consider, am I seeing something that is working better for outcomes using 4 mg versus 2 mg during that PRN phase. 15:37:40 15:37:44 15:37:49 15:37:54

Q If we could turn back to the previous page, you have a Table 4 that you've included. If you can take a look at that. 15:37:55 15:37:59 15:38:02

Now, I have to admit, I have a color 15:38:06

copy. I see that you don't. If you want to look at the color copy that I handed you this morning, feel free to, but I'm going to refer to colors. I just want to make sure you -- 15:38:09 15:38:12 15:38:15 15:38:18

A Oh, if you're going to refer to colors, I have to look at it. 15:38:20 15:38:22

Q It might be easier to do that, but it's on page 62. 15:38:24 15:38:26

A Thank you. 15:38:29

THE WITNESS: I didn't mean to talk over her. Okay. 15:38:31 15:38:33

BY MS. CHACON: 15:38:33

Q Okay. So what we were just discussing with respect to your opinion in paragraph 124, so that is -- you're suggesting the POSA would have compared the first blue line 2 mgs, Q4 to the bottom line in red, which is 4 mgs, Q12. 15:38:33 15:38:37 15:38:41 15:38:45 15:38:49

Am I understanding your opinion correctly? 15:38:56 15:38:58

A That would be one of the comparisons. The reason I put the table in, as I explained, is to look at the comparisons across all of these 15:38:58 15:39:00 15:39:01

doses because there's an inconsistency across all the doses. 15:39:04 15:39:07

Q Okay. So -- but you're saying that the person of skill in the art would have first thought to look at the 2-mg Q4 versus the 4-mg Q12 data. Am I understanding that? 15:39:08 15:39:10 15:39:13 15:39:17

MS. KAYALI: Sorry. Objection. Mischaracterizes testimony. Lacks foundation. 15:39:21 15:39:23

You can answer. 15:39:25

THE WITNESS: I didn't say they would look at that first. I said that they would consider whether to pursue a high-dose aflibercept product would have compared the PRN phase results of the study participants in the 4 mg quarterly arm to the 2 mg monthly arm and additional information thereafter in the paragraph. 15:39:28 15:39:29 15:39:32 15:39:34 15:39:36 15:39:38 15:39:41

BY MS. CHACON: 15:39:44

Q Okay. And some of the additional information that's available in this table are other arms where different doses of aflibercept are administered in Q12; is that right? 15:39:44 15:39:46 15:39:49 15:39:53

In Table 4? 15:40:03

A I would say it's showing where other doses are given and where other frequency in the initial 12 weeks are given. 15:40:05 15:40:07 15:40:17

Q Okay. So in the second yellow line, that's .5 mgs of aflibercept administered quarterly; is that correct? 15:40:20 15:40:24 15:40:29

A Just to emphasize, administered quarterly in the first 12 weeks of the study, but administered as-needed in 12 to 52 weeks of the study as all the other arms could be administered as-needed in weeks 12 to 52. I just wanted to emphasize. 15:40:30 15:40:34 15:40:37 15:40:41 15:40:43 15:40:47

Q Fair enough. 15:40:48

And is that also the case with the next line down, the 2-mg Q12, so quarterly but then as needed thereafter? 15:40:48 15:40:51 15:40:56

A That's correct. 15:40:58

Q And then, again, the same thing for the 4 mgs, quarterly, and then as needed thereafter? 15:40:58 15:41:01

A That's correct. 15:41:11

Q Okay. So we have three arms here where they are being administered quarterly and then as 15:41:11 15:41:13

needed thereafter. 15:41:17

Would a person of skill in the art look 15:41:18

to the comparison of all three of those quarterly 15:41:21

arms to understand whether or not to pursue a 15:41:24

high-dose aflibercept product? 15:41:28

A I think they would consider that 15:41:33

information in addition to the first two as well. 15:41:35

I highlighted the whole table for that reason and 15:41:39

not just three rows of the five rows that are 15:41:42

there. 15:41:49

Q And one of the reasons they might do 15:41:49

that is because those three are all on the same 15:41:51

dosing regimen. 15:41:54

Would you agree with that? 15:41:56

MS. KAYALI: Objection. Vague. 15:41:57

You can answer. 15:42:00

THE WITNESS: I don't know why they 15:42:06

would look just at those three. As I said, they 15:42:07

would look at all five rows to integrate what was 15:42:10

going on in terms of, for example, the mean 15:42:15

number of days to first injection over the PRN 15:42:18

phase. 15:42:23

BY MS. CHACON: 15:42:23

Q Sure. And I'm not suggesting they would look at that to the exclusion of the rest of the data. I just want to make sure that you're clear in my question. 15:42:24 15:42:26 15:42:29 15:42:29

My question is simply: One of the reasons that they might look at those three arms at the bottom of the table -- the bottom three arms is because they're all on a quarterly and then PRN basis. 15:42:30 15:42:32 15:42:36 15:42:38 15:42:41

Would you agree with that? 15:42:45

MS. KAYALI: Objection. Vague. Lacks foundation. 15:42:46 15:42:47

You can answer. 15:42:48

THE WITNESS: Again, I would say that they're going to look at all five rows and not just the three that started with Q12 in the beginning. 15:42:53 15:42:54 15:42:59 15:43:04

BY MS. CHACON: 15:43:05

Q So you can't answer my question as to whether or not a person of skill in the art would look at those three arms because they have the 15:43:05 15:43:17 15:43:19

same dosing regimen? 15:43:22

MS. KAYALI: Objection. Asked and 15:43:25

answered. 15:43:26

THE WITNESS: I think they would look at 15:43:30

those three arms in conjunction with the other two 15:43:31

rows above it. 15:43:37

BY MS. CHACON: 15:43:37

Q Okay. Now, if we're looking at the 15:43:37

quarterly arms for a moment and comparing those 15:43:40

three rows, which of the groups exhibited the 15:43:42

lowest mean number of injections over the PRN 15:43:47

phase? 15:43:50

A Numerically, the lowest mean number 15:43:57

was 1.7 in the 4-mg Q12. 15:44:01

Q Okay. Looking at the mean number of 15:44:07

days to first injection over PRN phase, which one 15:44:11

of those three quarterly groups exhibited the 15:44:16

highest mean number of days to first injection 15:44:18

over the PRN phase? 15:44:21

A Numerically, the 4 mg Q12 was 138 15:44:24

compared, for example, with the .05-mg Q12, which 15:44:25

was very close at 133. 15:44:31

Q Okay. Now, looking at the mean number of days to first injection over PRN phase, which one of those quarterly dosing arms had the highest number of -- or median number of days to first injection over PRN phase? 15:44:34 15:44:37 15:44:41 15:44:45 15:44:50

A Numerically the 4 mg Q12 had the highest number, which was still lower than, for example, the second row of the 2 mg Q4. 15:44:52 15:44:56 15:45:00

Q But it's the highest of all the regiments that are evaluated the same dosing regimen; correct? 15:45:04 15:45:06 15:45:10

MS. KAYALI: Objection. Lacks foundation. Mischaracterizes testimony. 15:45:11 15:45:13

You can answer. 15:45:15

THE WITNESS: Numerically, it's the highest of the three rows there at Q12. 15:45:16 15:45:19

BY MS. CHACON: 15:45:24

Q And just to make sure I'm clear for -- for all of these groups, how long was the treatment regiment before the PRN group was started? 15:45:25 15:45:27 15:45:30 15:45:32

A I'm not sure I understand what you mean 15:45:40

by "how long." I will say that, in the Q4 group, they were treated at baseline four weeks and eight weeks. And in the Q12 group, they were treated at baseline. 15:45:42 15:45:47 15:45:50 15:45:57

And then at 12 weeks they were all given an injection, and thereafter they were followed as needed on a Q four-week basis. 15:45:58 15:46:00 15:46:05

Q Understood. I apologize. I think I probably answered my own question looking at paragraph 118 in your report. So if you include there during PRN phase that took place from weeks 16 to 52. 15:46:08 15:46:09 15:46:12 15:46:17 15:46:20

So does that mean the first phase took place weeks 1 to 15? 15:46:22 15:46:24

A The authors, in my reviewing these papers, were not clear in my mind as to when visual acuities were obtained and considered part of the primary outcome the first 12 weeks, compared with the PRN phase because there was an injection given at week 12 after the primary endpoint visual acuity was measured. And then the first follow-up of that injection given at week 12 15:46:31 15:46:34 15:46:42 15:46:46 15:46:52 15:46:56 15:47:00 15:47:04

was at week 16.

And -- so it's not super clear from the design of the study when they might consider the end for visual acuity.

That's clear, but does that mean the PRN started the second after the visual acuity was measured for week 12 and before the injection that week 12 was given.

Q Now, looking at -- I'm focused on sort of the phase of the trial before the PRN phase -- however long that was.

Is it fair to say that the group who received 2~mg quarterly were given more injections than the groups that received aflibercept quarterly -- I'm sorry -- not quarterly -- every four weeks? Let me start that over to make sure the question is clear. Okay? Rewind. All right.

So looking at the phase before the PRN phase, is it fair to say that the group who received 2~mg every four weeks was given more injections than the group that received the aflibercept doses quarterly?

A Yes. 15:48:39

Q Do you have an understanding of how much additional drug that might mean that the patient received for the monthly 2 mg group as compared to the quarterly groups? 15:48:40 15:48:42 15:48:46 15:48:50

A Two additional doses spread four weeks apart. 15:48:52 15:48:55

Q All right, Dr. Bressler. I'm going to move on to Section F on -- beginning on page 68 of your declaration. 15:50:33 15:50:35 15:50:46

A Okay. One moment, please. 15:50:54

Q Sure. 15:50:57

A Thank you. 15:50:59

MS. KAYALI: Actually, Counsel, if we're moving on to a different section, I could really use a break. So we could do that and hopefully that will bring us home. 15:51:00 15:51:02 15:51:03 15:51:05

THE WITNESS: That would be great for me if we can go right from there to the end when we come back, only because I'm going to run to the bathroom as well. Okay? 15:51:07 15:51:08 15:51:11 15:51:13

MS. CHACON: Sure. We can go off the 15:51:14

record. 15:51:15
THE WITNESS: Okay. 15:51:16
THE VIDEOGRAPHER: We are going off the 15:51:17
record. The time is 15:51. 15:51:18
(Recess.) 15:51:21
THE VIDEOGRAPHER: We are going back on 16:11:18
the record. The time is 16:11. 16:11:19
BY MS. CHACON: 16:11:22
Q Dr. Bressler, before the break, I was 16:11:22
pointing your attention now to your Section F that 16:11:30
begins on -- on page 68, if you want to head that 16:11:32
way, please. 16:11:37
A Yes. Thank you. Okay. I'm ready. 16:11:38
Thank you. 16:12:25
Q Uh-huh. All right. So in this section, 16:12:25
you are detailing some clinical studies of 16:12:30
anti-VEGF molecules after aflibercept; is that 16:12:34
correct? 16:12:42
A That's correct. After aflibercept 2 mg. 16:12:43
Q Okay. And when we say "after 16:12:46
aflibercept," as we're reading context in your 16:12:48
report, in paragraph 134, you're referring to 16:12:52

after May 2018? 16:12:54

MS. KAYALI: Objection. Lacks 16:13:00

foundation. 16:13:01

THE WITNESS: So I'm just looking at the 16:14:02

dates. Abicipar is after 2018 -- 16:14:04

BY MS. CHACON: 16:14:12

Q Uh-huh. 16:14:12

A -- and I have to look at the other one, 16:14:13

Beovu. 16:14:15

As is the Beovu, yes. Thank you. Yes, 16:14:24

after 2018. 16:14:26

Q Okay. So you're discussing two 16:14:28

anti-VEGF drugs here that are post-May 2018. Is 16:14:29

that accurate? 16:14:34

A I'm discussing results from trials with 16:14:36

those that are post-May 2018. That -- that's 16:14:39

correct. 16:14:44

Q Okay. Now, we were discussing earlier 16:14:45

today some of the scientific characteristics of 16:14:48

aflibercept, for example, the fact that it's a 16:14:52

recombinant fusion protein. 16:14:55

Do you recall that? 16:14:59

A I do recall that. 16:15:00
Q And are you familiar with what kind of 16:15:01
drug abicipar is? 16:15:03
A Abicipar is a fusion protein, but it's a 16:15:09
much smaller non-glycosylated molecule at 34 16:15:10
kilodaltons, whereas aflibercept has a molecular 16:15:10
weight of 115 kilodaltons. 16:15:10
Q And were you aware of that prior to your 16:15:19
participation in this proceeding? 16:15:22
A In the deposition? 16:15:27
Q In -- I'm sorry. In this case, in this 16:15:29
matter, were you aware of what kind of molecule 16:15:32
abicipar was? 16:15:34
A I had read that previously and had heard 16:15:37
that previously and had never committed it to 16:15:40
memory and would have to look up what the 16:15:43
composition of both abicipar and brolucizumab 16:15:49
were. 16:15:51
Q Are you familiar with the type of 16:15:55
molecule that's a DARPn protein, D-A-R-P in 16:15:56
capitals, and little N? 16:16:04
A I've heard that term. And, again, in 16:16:07

the basic laboratory arena, I have a general understanding of that, and even perhaps believe that abicipar may fall into a DARPn molecule, but I'm not 100 percent certain. 16:16:09 16:16:12 16:16:16 16:16:23

Q Is a DARPn molecule a recombinant fusion protein? 16:16:25 16:16:27

A I would have to look it up. 16:16:28

Q All right. So let's look at paragraph 137 where you discuss Beovu -- I don't know if I'm saying that correctly, but brolucizumab. 16:16:33 16:16:38 16:16:45 16:16:47

Now, you opine here that brolucizumab is another example of failed efforts to obtain longer duration of effect by increasing dose; is that correct? 16:16:50 16:16:54 16:16:58 16:17:06

A That is correct. 16:17:06

Q Okay. Now, do you know what kind of molecule brolucizumab is? 16:17:07 16:17:12

A Only to say if I looked it up in the past and looked it up now, it's a lower weight anti-VEGF molecule. 16:17:19 16:17:22 16:17:27

Q Do you know whether or not brolucizumab 16:17:29

is a fusion protein? 16:17:33

A I don't know. I don't think it is, but 16:17:34

I don't -- I don't recall. 16:17:36

Q And brolucizumab has a different 16:17:38

molecular weight than aflibercept does; is that 16:17:41

correct? 16:17:44

A I would have to compare the molecular 16:17:48

weight of one, which is shown here, to the 16:17:51

molecular weight of aflibercept. I don't have 16:17:54

that committed to memory. 16:17:57

Q Okay. Well, I think you had just 16:17:58

mentioned that abicipar was a much smaller 16:18:00

molecule than aflibercept, and it looks like it 16:18:03

has a molecular weight of 34 kilodaltons, which 16:18:06

you report in paragraph 135 -- 16:18:10

A Very good. 16:18:13

Q -- in paragraph 137, you report 26 16:18:13

kilodaltons for brolucizumab, so I take it you'd 16:18:15

agree it's a smaller molecule, then? 16:18:17

A Now I do as an example of being able to 16:18:20

be comfortable looking up those things, but not 16:18:22

having more than a general understanding of them 16:18:24

until I look it up. 16:18:27

Q Do you understand or did you evaluate -- 16:18:30

probably a better word. Did you evaluate whether 16:18:33

or not there are any other molecular differences 16:18:36

between aflibercept and brolucizumab? 16:18:39

MS. KAYALI: Objection. Vague. 16:18:41

THE WITNESS: I didn't evaluate that 16:18:48

because, typically, I look at, from a clinician's 16:18:49

point of view and clinical research point of view, 16:18:58

the subsequent results of using these agents, not 16:19:00

the -- the laboratory differences among these 16:19:05

agents. 16:19:11

BY MS. CHACON: 16:19:12

Q Did you consider whether any of the 16:19:12

differences between the aflibercept and 16:19:16

brolucizumab -- the difference in the type of 16:19:20

molecule it is, the type of drug it is would have 16:19:23

any effect on safety or efficacy? 16:19:26

A Only to the degree that, if they are 16:19:29

different, then they need to be monitored 16:19:33

carefully as to whether they may have different 16:19:36

safety or efficacy in the clinical trial, in the 16:19:38

human being who has the disease of interest that's being studied. 16:19:42 16:19:44

Q Now, in the middle of paragraph 137, you say, "Unlike abicipar, brolucizumab was approved by FDA for administration at a 6-mg dose at 128-mg per mil concentration, but its sponsor had to discontinue multiple clinical trials due to inflammation and vision loss." 16:19:50 16:19:54 16:19:58 16:20:03 16:20:08 16:20:10

Do you see that? 16:20:12

A I do. 16:20:14

Q Okay. And what's the basis for your statement here that "the sponsor had to discontinue multiple clinical trials due to inflammation and vision loss"? Do you recall? 16:20:14 16:20:19 16:20:21 16:20:23

A There were several clinical trials that were listed on clinicaltrials.gov by the company -- it might be Novartis. 16:20:27 16:20:31 16:20:37

I'm trying to recall, but whatever company was doing it where they chose to discontinue those trials when they noted the extensive inflammation and vision loss that was being reported in the clinical practice setting 16:20:45 16:20:47 16:20:49 16:20:54 16:20:57

where it was now being used. 16:21:01

Q Was the observed inflammation and vision loss observed in all of the dosing arms that were evaluated in those trials? 16:21:05 16:21:08 16:21:13

A I can't recall. What I do recall is that the inflammation that was seen was at first identified in the clinical practice setting. 16:21:18 16:21:21 16:21:27

There was some retrospective attempts in evaluation to look at what inflammation existed in the clinical trials in order to try to come up with why it happened, which was not able to be discovered or determined. 16:21:30 16:21:34 16:21:38 16:21:43 16:21:46

Q And I think in that sentence you make reference to Exhibit 2032. Do you recall what that exhibit is? 16:21:54 16:21:56 16:22:03

A I do. 16:22:17

Q And what is it? 16:22:17

A It was a press release by Novartis on the one-year results of their phase three MERLIN study looking at Beovu with four-week dosing. And a general update on what was going on with their clinical trial program. 16:22:22 16:22:26 16:22:26 16:22:30 16:22:33

Q So I'll introduce what's already been entered in this proceeding as Regeneron Exhibit 2032. 16:22:39 16:22:43 16:22:45

(Petitioner's Exhibit 2032 was marked for identification, the original of which is attached hereto.) 16:22:47 16:22:47 16:22:47

THE WITNESS: Thank you. 16:23:14

One moment. I'm just going to look at it now. 16:23:42 16:23:46

BY MS. CHACON: 16:23:47

Q Sure. 16:23:47

A I was just putting my paragraph into context. 16:23:48 16:23:50

Q Are you reading through the press release? 16:24:53 16:24:54

A I am, and as I got halfway through, I wanted to remind myself of when it was done, so I was just looking at the date, which was 2021. 16:24:55 16:24:58 16:25:00

Okay. Thank you. 16:25:22

Q Sure. 16:25:23

A I'm ready. 16:25:24

Q Okay. Now I want to draw your attention 16:25:24

to page 2 of the press release, and it's the second full paragraph starting with "Novartis evaluated." 16:25:26 16:25:29 16:25:37

Are you there? 16:25:37

A Almost. 16:25:38

Q Okay. 16:26:05

A Okay. The "although" paragraph? 16:26:09

Q No. The one below it. 16:26:11

A Okay. 16:26:12

Q The "Novartis evaluated it." 16:26:13

Now, is it true that Novartis ended the brolucizumab trials only for the four-week dosing interval? 16:26:13 16:26:17 16:26:20

A And now please repeat your question. 16:26:38

Q Is it true that Novartis ended these clinical trials only for the four-week dosing interval? 16:26:40 16:26:44 16:26:48

A I don't have evidence from this as to their making that decision based only on the four-week dosing. 16:26:57 16:26:59 16:27:06

Q Well, in the bottom of the paragraph that we were just looking at, the paragraph that 16:27:08 16:27:12

starts "Novartis evaluated" -- 16:27:14

A Uh-huh. 16:27:20

Q -- the last sentence there, Novartis, 16:27:20

says, "Physicians should not treat patients with 16:27:20

Beovu 6 mg at intervals less than two months 16:27:21

beyond the first three doses." 16:27:25

Do you see that? 16:27:26

A I do. 16:27:28

Q So isn't that Novartis telling 16:27:28

physicians that they should consider to administer 16:27:32

Beovu so long as it's at intervals that are no 16:27:34

less than two months beyond the first three doses? 16:27:39

A No, it's saying that physicians should 16:27:41

not treat patients with Beovu at intervals less 16:27:41

than two months beyond the first three doses. 16:27:44

Q Isn't that what I just said? 16:27:49

A I didn't hear it that way. You can 16:27:51

repeat it. 16:27:51

Q Okay. I said isn't Novartis telling 16:27:51

physicians that they should not treat patients at 16:27:53

intervals less than two months beyond the first 16:27:56

three doses, meaning that they can treat when it's 16:27:58

two months or more? 16:28:02

A That was the difference. They didn't 16:28:04

say meaning that you can treat them when it's two 16:28:05

months or more. They did not say that. 16:28:08

Q Okay. So what would you understand 16:28:10

the -- what would you understand them to be 16:28:11

saying, then, in that sentence? 16:28:15

A That you should not treat patients at 16:28:18

intervals less than two months beyond the first 16:28:20

three doses. 16:28:24

Q So you don't read that to suggest that 16:28:26

you can still administer a Beovu 6 mgs so long as 16:28:28

it's not less than two months? 16:28:32

A Not from what they said here. 16:28:35

Q Okay. And go down -- not the next 16:28:37

paragraph, but the paragraph after that starts, 16:28:41

"When used"? 16:28:43

A Uh-huh. 16:28:45

Q They say, "When used on a two to 16:28:46

three-month interval following the loading phase, 16:28:48

Beovu continues to be an important and effective 16:28:48

treatment option for appropriate patients with wet 16:28:51

AMD."

Do you see that?

A I do.

Q Okay. What do you understand Novartis to be suggesting there?

A That in their opinion, as the people who market this agent, their opinion is that it continues to be an important effective treatment option for appropriate patients with wet AMD.

Q When it's used on a two or three-month interval following the loading phase; correct?

A Correct. That is their opinion.

Q Right. So they're telling people that you can still continue using Beovu so long as it's on a two to three-month interval following the loading phase; right?

A Well, they're not telling people to use it, but they're saying, in their opinion, after the loading phase it continues to be an important and effective treatment option for appropriate patients with wet AMD.

And I can recall when this was going on

that wasn't the opinion of most physicians. Most physicians concluded, if that's a problem, whenever they're seeing it, and if it's a problem in the clinical practice setting as cases are being presented, that, in the POSA's opinion, they would not want to continue using this, and that became reflected in the sales they had of brolucizumab soon thereafter. 16:29:49 16:29:54 16:29:58 16:30:00 16:30:03 16:30:09 16:30:12 16:30:14

Q Okay. So just to be clear, you're pointing to this press release as supportive of the opinion that a person of skill in the art would have been taught away from higher doses of aflibercept. 16:30:16 16:30:18 16:30:21 16:30:23 16:30:27

So you're relying on it for the fact that the four-week dose was discontinued, but not acknowledging the fact that it also says that you can continue to use the drug for two to three-month intervals. 16:30:28 16:30:30 16:30:35 16:30:39 16:30:42

Is that accurate? 16:30:44

MS. KAYALI: Objection. Lacks foundation. 16:30:45 16:30:47

THE WITNESS: I was using it as an 16:30:56

example of a failed effort to obtain longer duration of effect by increasing the dose. 16:30:57 16:31:00

BY MS. CHACON: 16:31:02

Q So you're relying on the press release that says, "Don't use this drug every four weeks, but continue to use it or you can use it for every two to three-month intervals going forward"; right? 16:31:02 16:31:04 16:31:09 16:31:12 16:31:16

A Not right. Looking at the totality of the clinical trial portfolio of Beovu and the inflammation that would seem to outweigh any benefits, I looked at that safety as being an example of failed effort to obtain longer duration of effect by increasing the dose because of the safety issue. 16:31:16 16:31:20 16:31:25 16:31:30 16:31:32 16:31:35 16:31:37

Q But you relied on this press release, though, in your opinion; correct? 16:31:38 16:31:41

And again, for what it's worth, you cite to it on paragraph 137 on page 70 of your report. 16:31:59 16:31:59

A I rely on this press release and the clinical trials that it refers to and the results in those clinical trials that it refers to and in 16:32:04 16:32:07 16:32:10

addition to the higher intraocular information that then was reported in Exhibit 2024 in the HAWK and HARRIER studies. 16:32:15 16:32:19 16:32:24

Q Let's see. I want to point you now, Dr. Bressler, to page 94 of your declaration in paragraph 178. 16:33:02 16:33:04 16:33:08

A Okay. One moment, please. 16:33:10

Okay. Thank you. 16:33:47

Q Okay. So on paragraph 178, you are addressing the Lehman presentation, which Dr. D'Amico relies upon, and you say that the Lehman presentation is a slide deck that does not report full study data. 16:33:48 16:33:52 16:33:56 16:34:02 16:34:06

Now, you reviewed the Lehman presentation in forming your opinions or -- I should say in preparing for your deposition today? 16:34:08 16:34:11 16:34:16

A I -- I did review it in preparing for the deposition. 16:34:18 16:34:20

Q Okay. And do you understand that the Lehman presentation is a presentation that was presented by Regeneron on March 8th, 2006? 16:34:21 16:34:22 16:34:25

A If I can look at it again. That's to 16:34:30

the best of my recollection, that it was a presentation by Regeneron. 16:34:33 16:34:37

Q Sure. Let's do that. So we're going to hand you what has already been entered in this proceeding as Alvotech Exhibit 1030. 16:34:38 16:34:40 16:34:44

THE WITNESS: Thank you. 16:34:46

(Petitioner's Exhibit 1030 was marked for identification, the original of which is attached hereto.) 16:34:47 16:34:47 16:34:47

THE WITNESS: Thank you. Yes, this was a Regeneron presentation. 16:35:04 16:35:15

BY MS. CHACON: 16:35:16

Q Okay. Now, this presentation was given at the Lehman Brothers 9th Annual Global Health Care conference. 16:35:16 16:35:24 16:35:26

Are you familiar with that conference? 16:35:27

A I vaguely know that there are a few groups such as Lehman Brothers or JP Morgan that have annual conferences to bring together various companies in the health field. 16:35:31 16:35:35 16:35:39 16:35:46

Q Did you understand what the purpose of those conferences are? So, for example... 16:35:49 16:35:50

A I believe -- 16:36:01
Q I'm sorry. Go ahead. 16:36:01
A No, you go. 16:36:03
Q I was just going to give an example. So 16:36:03
for example, you know, JP Morgan is one in which 16:36:05
companies go to try to gain investors for their 16:36:09
company or, you know, enter into partnerships with 16:36:13
other companies. 16:36:15
What is your understanding of what the 16:36:16
Lehman Brothers Global Healthcare Conference is 16:36:18
meant to achieve? 16:36:21
A I thought, without any attendance to it 16:36:22
or expertise, that it was the same purpose, to 16:36:26
reach out to investors -- Uh-huh. 16:36:31
Q All right. So in -- in this 16:36:38
presentation on slide 18 -- or page 18, there's a 16:36:44
slide addressing Phase 1 intravitreal trial. 16:36:52
Do you see that? 16:36:57
A I do. 16:37:03
Q And Regeneron is reporting on status 16:37:03
and preliminary results in bullet 3, identifies 16:37:05
the dose levels that were completed, which 16:37:08

includes .05, .15, .5, 1, 2, and 4 mgs of aflibercept. 16:37:10 16:37:20

And that they say, "All planned dose levels completed. Maximum tolerated dose not reached." 16:37:20 16:37:22 16:37:25

Do you see that? 16:37:26

A I do. 16:37:27

Q Now, your declaration in paragraph 178, you criticize the Lehman presentation as "omitting all relevant data such as baseline visual acuity, retinal thickness, and subject outcomes preventing a POSA from drawing any conclusion as to whether the maximum tolerated dose was reached." 16:37:28 16:37:31 16:37:37 16:37:41 16:37:44 16:37:48

Do you see your opinion there? 16:37:51

A I do. 16:37:52

Q All right. So it -- is it your opinion that a person of skill in the art wouldn't be able to draw any conclusion, zero, about maximum tolerated dose based on Regeneron's representations at the Lehman Brother's conference? 16:37:53 16:37:56 16:37:58 16:38:04 16:38:08 16:38:11

A That is my opinion. 16:38:11

Q Okay. 16:38:13
MS. KAYALI: Objection. Argumentative. 16:38:14
You can answer. 16:38:15
THE WITNESS: That is my opinion. 16:38:20
BY MS. CHACON: 16:38:21
Q Now, given the fact that this is being 16:38:21
presented to, I have to assume a wide audience at 16:38:25
a global healthcare conference, do you think that 16:38:29
Regeneron would lie that the maximum tolerated 16:38:33
dose was not reached? 16:38:35
MS. KAYALI: Objection. Argumentative. 16:38:37
You can answer. 16:38:39
THE WITNESS: I don't think it would 16:38:44
lie. I said it "omits all the relevant data, such 16:38:44
as baseline visual acuity, retinal thickness, and 16:38:47
subject outcomes that would prevent a POSA from 16:38:50
drawing any conclusion as to whether was indeed 16:38:55
reached." 16:38:59
BY MS. CHACON: 16:38:59
Q So you're saying a POSA would not take 16:38:59
Regeneron at its word that the maximum tolerated 16:39:03
dose was not reached for aflibercept based on this 16:39:06

Phase 1 trial? 16:39:09

MS. KAYALI: Objection. Lacks 16:39:10

foundation. Mischaracterizes testimony. 16:39:11

You can answer. 16:39:13

THE WITNESS: I think a POSA would want 16:39:15

all the relevant data, such as the examples I gave 16:39:17

of visual acuity, retinal thickness and subject 16:39:21

outcomes, and that this would omit that 16:39:23

information that a POSA would need to draw any 16:39:27

conclusion as to whether the maximum tolerated 16:39:31

dose was indeed reached. 16:39:34

BY MS. CHACON: 16:39:36

Q Now, you know if Regeneron was not being 16:39:36

truthful about anything that it would present to 16:39:42

at a global healthcare conference like this to try 16:39:46

to secure investors, that would probably get the 16:39:49

company in some big trouble. 16:39:52

Would you agree with that? 16:39:54

MS. KAYALI: Objection. Outside the 16:39:55

scope of Dr. Bressler's direct testimony. 16:39:55

Argumentative. And calls for a legal conclusion. 16:39:55

THE WITNESS: It is outside of the scope 16:40:01

of my knowledge of what the rules are. I believe that they cannot lie at their presentations. 16:40:02 16:40:06

BY MS. CHACON: 16:40:32

Q Dr. Bressler, I'd like you to pull back Vitti -- 16:40:32 16:40:41

A Uh-huh. 16:40:42

Q -- which was Alvotech Exhibit 1007. 16:40:42

A One moment, please. 16:41:11

Q Sure. And I'm not meaning to rush you, Doctor, but I'm actually just going to ask you some information about what's on the cover of the Vitti patent publication. 16:41:13 16:42:08 16:42:10 16:42:12

A Thank you. I'm ready now. 16:42:13

Q Okay. All right. So you have Vitti back in front of you, and you see here for Vitti that the applicant is listed as Regeneron Pharmaceuticals, Inc.? 16:42:16 16:42:16 16:42:19 16:42:22

A Yes. 16:42:24

Q And the same for the assignee of this patent publication -- patent application publication? 16:42:25 16:42:27 16:42:30

A Yes. 16:42:30

Q Okay. So you understand that Vitti is a Regeneron document? 16:42:31 16:42:34

A Yes. 16:42:37

Q Now, earlier we were looking at paragraph 139 in Vitti regarding what the Regeneron inventors disclosed regarding dose. 16:42:41 16:42:46 16:42:58

A One moment. 16:43:01

Q Sure. 16:43:02

A Okay. Thank you. 16:43:39

Q Now, earlier when we talked about this paragraph, we had said that this states -- discloses .05 mgs to about 10 mgs of a VEGF antagonist, (ergo aflibercept.) 16:43:41 16:43:46 16:43:50 16:43:53

Do you recall that discussion? 16:43:58

MS. KAYALI: Objection. Lacks foundation. 16:43:59 16:43:59

You can answer. 16:44:01

THE WITNESS: It says, "In certain embodiments, .05-mg, 1 mg, 3 mg or 6 mg of an antibody is administered in combination with .05 mgs to about 10 mgs of a VEGF antagonist," for example, aflibercept. 16:44:03 16:44:03 16:44:09 16:44:14 16:44:20

BY MS. CHACON: 16:44:23

Q Okay. Now, earlier today, Dr. Bressler, 16:44:23

I had asked you if you're familiar with patents, 16:44:30

and you had mentioned that you're an inventor on a 16:44:32

patent. 16:44:35

Do you recall that? 16:44:35

A I do recall that. 16:44:36

Q Okay. Do you have an understanding that 16:44:37

inventors have a duty to be honest with the U.S. 16:44:39

Patent and Trademark Office? 16:44:44

A I would assume so. 16:44:46

Q Okay. And is there any reason that you 16:44:48

have to believe that Regeneron was not being 16:44:55

honest with the Patent Office when it said in 16:44:57

paragraph 139 that in certain embodiments, that 16:44:59

you can administer .05-mgs, 1 mg, 3 mgs or 6.0 mgs 16:45:04

of an anti-angiogenic antibody administered in 16:45:04

combination with .05 mgs to about 10 mgs of VEGF 16:45:13

antagonist (ergo aflibercept)? 16:45:15

MS. KAYALI: Objection. Lacks 16:45:20

foundation. Calls for speculation. 16:45:22

You can answer. 16:45:24

THE WITNESS: I have no reason to believe they would be dishonest with that statement. 16:45:27 16:45:27 16:45:30

BY MS. CHACON: 16:45:35

Q So you believe that they would truthfully be telling the Patent Office that they, at this time, had disclosed and invented aflibercept in a range of .05 mgs to about 10 mgs? 16:45:35 16:45:36 16:45:39 16:45:40

MS. KAYALI: Objection. Lacks foundation. Calls for a legal conclusion. 16:45:48 16:45:49

THE WITNESS: Again, given the complexity of patents, I can just tell you that, in this dosage section, they stated, "In certain embodiments, .05-mg, other doses, here up to 6 mg of an anti-angiogenic" -- "two antibodies are administered in combination with point .05 mg to about 10 mg of a VEGF antagonist," for example. 16:45:54 16:45:55 16:45:58 16:46:01 16:46:08 16:46:10 16:46:13

BY MS. CHACON: 16:46:15

Q Okay. So at least it's fair that we take Regeneron at its word that what it's disclosed in paragraph 139 is truthful and accurate. 16:46:15 16:46:18 16:46:21 16:46:24

Is that fair? 16:46:25

A I think that's fair. That is fair. 16:46:27

Q If you could go to paragraph 208 of your declaration, Dr. Bressler, which is on page 112. 16:47:01 16:47:04

A Okay. One moment. One moment, please. 16:47:07

Q Sure. And when you're ready, I just actually have a very basic question about patients with glaucoma. 16:47:29 16:48:32 16:48:35

A Very good. I'm almost done. 16:48:45

Okay. I'm ready. 16:48:47

Q Now, in paragraph 208, you're talking about some populations of patients receiving anti-VEGF treatment with coexisting conditions including glaucoma. 16:48:48 16:48:51 16:48:53 16:48:57

Do you have a sense of what percentage of patients receiving a VEGF antagonist have glaucoma? 16:48:58 16:48:59 16:49:07

A I would estimate, and I would go back to other sources that I could find readily on review that it would be perhaps 5 percent to 10 percent of some of these populations, such as the neovascular macular degeneration population, have 16:49:09 16:49:11 16:49:17 16:49:21 16:49:24

glaucoma. 16:49:29

Q I'm sorry. The condition was the 16:49:34

neovascular... 16:49:36

A Macular degeneration. Sorry. The wet 16:49:37

form of -- 16:49:37

Q Wet form, nAMD. Got it. 16:49:39

Okay. And do you have a sense of what 16:49:42

the percentage of patients would be for -- that 16:49:43

have glaucoma with respect to, like, diabetic 16:49:47

retinopathy or DME? 16:49:50

A It would probably be lower because 16:49:53

that's a younger age-group on average, so we would 16:49:54

be guessing right now, but the data I'm sure out 16:50:02

there, or could be, well-estimated by review, and 16:50:04

I would guess maybe 3 percent of the population 16:50:08

with diabetes have glaucoma. 16:50:12

Q Let's flip ahead in your declaration, 16:50:22

Dr. Bressler, to paragraph 210, which is on 16:50:24

page 114. 16:50:28

Are you there? 16:50:38

A Yeah. I just want to understand the 16:50:39

context. So I just need a minute. 16:50:41

Thank you. Thank you. 16:51:26

Q Sure. In paragraph 210, you say, 16:51:27

"Because of these known risks a POSA would have 16:51:31

preferred a volume not exceeding 50 mL, the 16:51:32

standard injection volume for all intravitreal 16:51:37

anti-VEGF protein formulations, including EYLEA 16:51:37

(2 mg), Lucentis, and off-label Avastin, unless 16:51:41

the benefits were proven to outweigh any risk in 16:51:49

clinical trials." 16:51:53

Do you see that? 16:51:54

A I do. 16:51:56

Q And I want to understand sort of the 16:51:56

scope of your opinion here. When you say, "Unless 16:51:57

the benefits were proven to outweigh any risks of 16:52:01

clinical trials," are you saying that a POSA would 16:52:04

not have considered or preferred a volume 16:52:09

exceeding 50 mL unless they eliminated or 16:52:10

outweighed any and all risks in clinical trials? 16:52:14

MS. KAYALI: Objection. Lacks 16:52:18

foundation. 16:52:19

You can answer. 16:52:21

THE WITNESS: It really depends on the 16:52:32

details of what the risks are and the benefits when other volumes were being tested. 16:52:33 16:52:38

BY MS. CHACON: 16:52:43

Q And I agree, and I'm trying to understand what risks you were contemplating when you wrote "unless the benefits were proven to outweigh any risks to clinical trials." 16:52:43 16:52:48 16:52:51 16:52:54

What were you referring to? 16:52:58

A Risks that would outweigh the benefits that were seen. 16:53:04 16:53:06

Q What would those be? 16:53:09

A For example, if a higher volume was associated with better visual acuity outcomes, and they were substantially better, the risks associated with a higher volume might be acceptable to say the benefits on the visual acuity outweigh the risks. 16:53:13 16:53:23 16:53:28 16:53:34 16:53:36 16:53:40

Q And when you say "higher volume," what kind of volume are you referring to? How much higher? 16:53:44 16:53:46 16:53:48

MS. KAYALI: Objection. Lacks foundation. 16:53:49 16:53:50

THE WITNESS: Any volume higher than the .05 milliliters that were being given millions of times around the world. 16:53:52 16:53:53 16:53:59

BY MS. CHACON: 16:54:01

Q Okay. So you are giving me an example of risks associated with higher volume. Are there any other risks that you're referring to here when you say "it has to outweigh any risks in clinical trials"? 16:54:01 16:54:21 16:54:26 16:54:28 16:54:32

MS. KAYALI: Objection. Asked and answered. 16:54:32 16:54:33

THE WITNESS: If, for example, there was increased pain from the increased volume being given and yet there were far greater visual acuity outcomes, then a POSA might be very comfortable with trying to get those people through the pain in some way, depending on how long it lasts, what the duration was, what the intensity was, to say, "But I'm going to be able to get so much better vision for you." 16:54:50 16:54:52 16:54:56 16:55:05 16:55:11 16:55:14 16:55:17 16:55:21 16:55:25

MS. CHACON: How much time do we have left on the record? 16:55:56 16:55:57

THE VIDEOGRAPHER: We are at six hours and 49 minutes. 16:55:59 16:56:01

MS. CHACON: All right. Let's go ahead and take a quick break. Let's take a five-minute break to see if I have anything else left, and then we'll come back. 16:56:02 16:56:04 16:56:07 16:56:10

THE WITNESS: Okay. Great. Thank you. 16:56:11

THE VIDEOGRAPHER: We are going off the record. The time is 16:56. 16:56:13 16:56:13

(Recess.) 16:56:17

THE VIDEOGRAPHER: We are going back on the record. The time is 17:08. 17:08:28 17:08:29

BY MS. CHACON: 17:08:32

Q Dr. Bressler, at the beginning of your deposition, I had asked you if there were any corrections you had made to your report, and you sort of mentioned, "I think there might be, but I can't quite remember where it was or what it was." 17:08:32 17:08:35 17:08:37 17:08:39 17:08:41

And now having sat through this proceeding, do you recall what correction, if any, that you were thinking of? 17:08:43 17:08:45 17:08:48

A I can't identify that one numerical 17:08:50

value which was off by one integer, like 22 instead of 23 or 23 instead of 22. 17:08:53 17:09:00

And I thought it was in relation to days, but I'd have to study it carefully to come up with that again. 17:09:03 17:09:04 17:09:07

Q Okay. And, during the course of your deposition today at any breaks, did you discuss the subject of your testimony with counsel? 17:09:09 17:09:11 17:09:14

A I did not. 17:09:16

MS. CHACON: Dr. Bressler, I don't have any further questions for you at this time subject to any redirect from your counsel. 17:09:20 17:09:21 17:09:23

THE WITNESS: Okay. 17:09:25

MS. KAYALI: Let's go off the record, and we'll do a brief break to consider any redirect and reconvene in maybe 10 minutes. 17:09:26 17:09:27 17:09:30

MS. CHACON: Sure. 17:09:34

THE WITNESS: Okay. 17:09:35

THE VIDEOGRAPHER: We are going off the record. The time is 17:09. 17:09:36 17:09:37

(Recess.) 17:09:41

THE VIDEOGRAPHER: We are going back on 17:18:26

the record. The time is 17:18. 17:18:27

EXAMINATION 17:18:28

BY MS. KAYALI: 17:18:30

Q And, Dr. Bressler, could you please open your declaration and turn to page 90? 17:18:30 17:18:33

And just let me know when you're ready. I don't want to rush you. 17:19:01 17:19:03

A Okay. Okay. I'm ready. 17:19:04

Q Okay. What is the difference, Dr. Bressler, as you've reflected in your opinions -- what is the difference between concentration and volume? 17:19:08 17:19:15 17:19:18 17:19:21

MS. CHACON: Object to form. Vague. 17:19:25

THE WITNESS: Volume is the total content of the fluid -- for example, 50 mL. Concentration is a dose divided by volume. 17:19:34 17:19:41 17:19:47

BY MS. KAYALI: 17:19:54

Q And -- so is dose different than or the same as or something else with respect to concentration? 17:19:54 17:19:57 17:20:00

MS. CHACON: Object to form. Compound. Vague. 17:20:01 17:20:02

THE WITNESS: Dose is a different measurement than concentration. 17:20:06 17:20:09

BY MS. KAYALI: 17:20:14

Q Okay. In your opinion, if a reference discloses a formulation of aflibercept that has a concentration of 80 mgs per milliliter, would the POSA interpret those words to be a dose of 8 mg aflibercept? 17:20:14 17:20:18 17:20:23 17:20:26 17:20:30

MS. CHACON: Objection. Vague. Calls for speculation. 17:20:34 17:20:36

THE WITNESS: The POSA, as we were just defining, would look at that as a concentration, not as a dose. 17:20:39 17:20:41 17:20:45

BY MS. KAYALI: 17:20:46

Q And that's true whether the concentration of 80 mgs per mil is reported in Vitti or in some other reference; right? 17:20:46 17:20:49 17:20:51

MS. CHACON: Objection to this question and the last questions as outside the scope of the direct testimony. 17:20:55 17:20:57 17:20:59

THE WITNESS: The concentration is a general scientific term that would apply to Vitti 17:21:00 17:21:02

or any of the other documents here that discuss concentration. 17:21:11 17:21:15

BY MS. KAYALI: 17:21:16

Q Okay. And so just to make sure whether my question is clear, whether it's Vitti or some reference that discloses a concentration of aflibercept of 80 mgs per mil, is your answer the same with respect to whether that's a disclosure of a dose of 8 mgs aflibercept? 17:21:16 17:21:19 17:21:20 17:21:22 17:21:27 17:21:29

MS. CHACON: Object to form. Objection. Outside the scope of the direct testimony. 17:21:31 17:21:32

THE WITNESS: My answer would be the same. 17:21:35 17:21:36

BY MS. KAYALI: 17:21:37

Q Oh. Could you turn to page 3 of your report in paragraph 1? 17:21:37 17:21:41

A One moment, please. Okay. Thank you. 17:21:56

Q Do you see this sentence -- it's the -- let's read the whole paragraph, I suppose. "I have been retained by counsel for Regeneron Pharmaceuticals, Inc., Regeneron as a technical expert in connection with the above captioned 17:22:16 17:22:20 17:22:23 17:22:25 17:22:26

proceeding." 17:22:29

Then you say, "I have been asked to 17:22:29

provide my opinions in connection with the 17:22:31

petition for post-grant review filed by Alvotech 17:22:33

USA, Inc., and Alvotech HF challenging Claims 1 17:22:36

through 38 of Regeneron's US Patent 17:22:41

No. 12,168,036. The '036 patent petition." 17:22:43

And then you say, "Including in 17:22:48

response to the declaration of Donald D'Amico, 17:22:49

Exhibit 1003 submitted in support of Alvotech's 17:22:52

petition." 17:22:56

Do you see that? 17:22:57

A I see that. 17:22:58

Q Okay. I'm going to mark what has 17:22:59

already been presented in this proceeding as 17:23:02

Exhibit -- Alvotech -- excuse me -- Exhibit 1003. 17:23:04

(Respondent's Exhibit 1003 was marked 17:23:10

for identification, the original of which is 17:23:10

attached hereto.) 17:23:10

MS. KAYALI: Oh, sorry. Thank you, 17:23:10

Madam Court Reporter. I should have handed that 17:23:10

to you. 17:23:10

BY MS. KAYALI: 17:23:32

Q And take your time, Dr. Bressler, but my question is just is this the declaration, Exhibit 1003, containing Dr. D'Amico's opinions to which you responded in your declaration? 17:23:32 17:23:34 17:23:36 17:23:41

A Yes. This is the declaration I'm referring to when I say "in response to the declaration of Dr. Donald D'Amico." 17:23:46 17:23:47 17:23:49

Q Okay. And can you turn to page 3 of Dr. D'Amico's declaration? And do you see the header "Roman 11" -- Roman XI -- "Ground 1"? 17:23:55 17:23:57 17:24:01

A I do. 17:24:11

Q Okay. And it -- header XI, Ground 1 reads, "Claims 1 and 4 through 38 are obvious over the combination of Vitti, AU label, and Larson"; right? 17:24:12 17:24:19 17:24:23 17:24:29

A Yes. 17:24:30

Q Okay. So did you understand Dr. D'Amico to be offering the opinion that claims 1 and 4 through 38 were obvious over the combination of Vitti, AU label, and Larson? 17:24:30 17:24:33 17:24:34 17:24:37

A I did. 17:24:39

Q Okay. And is that the obviousness theory to which you responded in your declaration -- or let me strike that and ask a better question. 17:24:40 17:24:42 17:24:45 17:24:48

Is that one of the obviousness theories to which you responded in your declaration? 17:24:48 17:24:49

A It is. 17:24:53

Q Okay. And if you turn to page 5 of Dr. D'Amico's declaration, do you see a header "Roman 7"? 17:24:54 17:24:56 17:25:00

A Page 5. 17:25:06

Q It's confusing. There are two page numbers. I'm looking at the -- 17:25:08 17:25:10

A Okay. I'm sorry. 17:25:12

Q That's okay. It's in the Table of Contents. There's a little four and a bigger five further down. 17:25:13 17:25:15 17:25:18

A A little four and bigger five later down. Okay. I'm on that page. 17:25:23 17:25:25

Q Okay. Do you see Roman 7? 17:25:27

A I see Roman 12. 17:25:29

Q Oh, excuse me. I've done that at least 17:25:31

three times in the last week. 17:25:33

Do you see Roman 12, which says Ground 2? 17:25:35

A I see Roman 12. 17:25:36

Q Okay. Thanks for rescuing me from embarrassment. 17:25:37

Ground two, as reflected in Roman 12 of Dr. D'Amico's declaration reads -- the header reads, "Claims 1 and 4 through 38 Are obvious over the combination of Regeneron's prior art (AU label), fielder and Larson"; right? 17:25:42

A Correct. 17:26:04

Q Okay. And is that another obviousness theory to which you responded in your declaration? 17:26:04

A It was. 17:26:07

Q Okay. So if you could -- sorry. Let me ask a better question. You understood -- did you understand -- strike that. 17:26:11

Did you understand Dr. D'Amico to be offering the opinion that Claims 1 and 4 through 38 are obvious over the combination of Regeneron's prior art, including Furfine, Dix, and AU EYLEA 17:26:16

17:26:19

17:26:20

17:26:23

17:26:27

17:26:30

label, Fiedler, and Larson? 17:26:33

MS. CHACON: Object to form. 17:26:37

Foundation. Vague. 17:26:38

THE WITNESS: I understood that. 17:26:40

BY MS. KAYALI: 17:26:41

Q Okay. And is that one of his opinions 17:26:41

to which you responded in your declaration? 17:26:45

A That is one of the opinions to which I 17:26:48

responded in my declaration with my opinion. 17:26:50

Q Okay. So could you flip back to page 3 17:26:53

of Dr. D'Amico's declaration? I apologize for 17:26:55

making you flip around. We're going back to Roman 17:26:59

11, where it referenced Ground 1. 17:27:02

A One moment. Okay. I'm there. 17:27:07

Q Okay. And if you turn now -- I'd ask 17:27:14

you to keep that page open -- 17:27:19

A Uh-huh. 17:27:21

Q -- and please turn to your own 17:27:21

declaration and look at paragraph 232 of your 17:27:23

declaration. 17:27:26

A Okay. 17:27:47

Q And do you see how, in -- in 17:27:48

paragraph 232, does the ground reported in the first row of the table that you've provided match Ground 1 as presented on page 3, Roman 11 of Dr. D'Amico's declaration? 17:27:49 17:27:55 17:28:00 17:28:05

A It does. 17:28:09

Q Okay. And if you stay on that page of your declaration and you flip to page 5 of Dr. D'Amico's declaration -- and now, again, looking at Roman 12, Ground 2. 17:28:10 17:28:13 17:28:17 17:28:21

Do you see that? 17:28:24

A I do. 17:28:25

Q Okay. If you compare what's written as Ground 2 in Dr. D'Amico's declaration to the second row of the table in paragraph 232, do you perceive a copy and paste error in reporting Ground 2 in your declaration? 17:28:26 17:28:29 17:28:33 17:28:38 17:28:41

A I do now. 17:28:43

Q Okay. And if you turn to page 73 -- perhaps -- 17:28:44 17:29:01

A Of my declaration? 17:29:02

Q Of your declaration. I apologize. Let's turn to actually page 72 of your 17:29:03 17:29:05

declaration. 17:29:07

Are you there? 17:29:11

A I'm there. 17:29:12

Q And do you see that that same table is 17:29:13

repeated on -- in paragraph 143? 17:29:15

A I do with the same copy and paste error. 17:29:19

Q Okay. And so if we turn back to page 5 17:29:26

of Dr. D'Amico's declaration reporting 17:29:29

Ground 12 -- excuse me -- Roman 12, Ground 2 -- 17:29:32

are you with me? 17:29:38

A I am. 17:29:39

Q Notwithstanding the copy/paste error 17:29:40

that was in the tables reporting the grounds in 17:29:43

your declaration, did you nonetheless respond to 17:29:45

Ground 2 as Dr. D'Amico set forth his opinions 17:29:48

with respect to the obviousness of the claims over 17:29:52

the combination of Regeneron's prior art Furfine, 17:29:54

Dix, AU EYLEA label, Fiedler and Larson? 17:29:57

MS. CHACON: Object to form. 17:30:03

Foundation. Leading. 17:30:05

THE WITNESS: I did respond. 17:30:06

MS. KAYALI: Okay. That's all the 17:30:09

questions I have for you, Dr. Bressler. I'm not sure if there will be any recross. 17:30:10 17:30:12

MS. CHACON: I actually have a couple quick questions just in response to that line of questioning that Counsel just asked you. 17:30:13 17:30:14 17:30:16

FURTHER EXAMINATION 17:30:18

BY MS. CHACON: 17:30:18

Q So I'm not going to have you go through your whole declaration again, Dr. Bressler, because I'm sure you want to get out of here, but the Furfine and Dix references -- if we wanted to understand what your opinions were addressing those references, could I just, for example, word search an electronic copy -- or -- of your report and look for Furfine and Dix -- would that be a fine way to figure out where you responded on those references? 17:30:18 17:30:22 17:30:26 17:30:29 17:30:35 17:30:37 17:30:39 17:30:43 17:30:47 17:30:49

MS. KAYALI: Objection. Lacks foundation. And outside the scope of the cross-examination -- or excuse me -- of the redirect testimony. 17:30:50 17:30:51 17:30:57 17:30:59

THE WITNESS: I think you'd have to take 17:31:01

that information in context of the entire declaration to -- 17:31:02 17:31:06

BY MS. CHACON: 17:31:08

Q Okay. 17:31:08

A -- understand my opinion on Ground 2. 17:31:09

Q Okay. And would it surprise you that just sitting here now doing a quick word search for Furfine and Dix in the body of your opinion, the only place that I see those references mentioned is in paragraph 42 of your declaration? 17:31:13 17:31:18 17:31:21 17:31:22 17:31:24

MS. KAYALI: Objection. Lacks foundation. Again, outside the scope of the redirect testimony. 17:31:30 17:31:30 17:31:34

THE WITNESS: I'd neither be surprised or not surprised. 17:31:37 17:31:38

BY MS. CHACON: 17:31:39

Q Okay. Do you recall what the Furfine and Dix references discuss? 17:31:39 17:31:41

A I'd have to go back to look at the exhibits. I remember them existing in the exhibits, so I remember that -- that term or that name. 17:31:50 17:31:52 17:31:54 17:31:58

Q Okay. Did you review those exhibits in preparation for your deposition today? 17:32:00 17:32:02

And for what it's worth, it's Exhibits 1005 and 1006. 17:32:07 17:32:09

A I did consider them in forming my opinion for the declaration. 17:32:19 17:32:21

Q My question was did you review those in preparation for your deposition today? 17:32:23 17:32:25

A Excuse me. I did not review those, that I recall, in preparation for the deposition today. 17:32:27 17:32:32

Q Okay. All right. 17:32:36

MS. CHACON: Thank you, Dr. Bressler. I don't have any further questions. 17:32:38 17:32:40

MS. KAYALI: No redirect, so you are a free man. 17:32:42 17:32:44

THE WITNESS: Thank you. 17:32:45

THE VIDEOGRAPHER: Stand by, and I'll go ahead and read us off the record. 17:32:46 17:32:47

This concludes the videotaped deposition of Neil M. Bressler. We are going off the record at 17:32. 17:32:49 17:32:51 17:32:56

(Deposition concluded at 5:32 PM.) 17:32:59

UNITED STATES PATENT AND TRADEMARK OFFICE)
)
BEFORE THE PATENT TRIAL AND APPEAL BOARD)

I am the WITNESS in the foregoing examination under oath. I have read the foregoing deposition and having made such changes and corrections as I desire, I certify that the same is true of my own knowledge, except as to those matters which are therein stated upon my information or belief, and as to those matters, I believe it to be true.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on _____

at_____.

_____

NEIL M. BRESSLER

CERTIFICATE OF SHORTHAND REPORTER

I, Bethany Woodward, a Certified Shorthand reporter, do hereby certify:

That Neil M. Bressler, the witness whose deposition is hereinbefore set forth, was duly sworn by me before the commencement of such deposition and that such deposition was taken before me and is a true record of the testimony given by such witness.

I further certify that the adverse party, Regeneron Pharmaceuticals, Inc., was represented by counsel at the deposition.

I further certify that the deposition of Neil M. Bressler occurred at the offices of Williams & Connolly LLP, at 680 Maine Avenue, SW, Washington, DC, on Thursday, September 10th, 2026, commencing at 8:09 a.m. to 5:32 p.m.

I further certify that I am not related to any of the parties to this action by blood or marriage, I am not employed by or an attorney to any of the parties to this action, and that I am in no way interested, financially or otherwise, in the

outcome of this matter.

WITNESS MY HAND THIS 11th day of September 2026.

Bethany Woodward
_____

Bethany Woodward

A Certified Shorthand Reporter

A
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