1 UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD
2

SAMSUNG BIOEPIS CO LTD,	)	
3	)	
Petitioner,	)	
4	)	Case No.
vs.	)	IPR2023-00933
5	)	Patent: 9,732,149
ALEXION PHARMACEUTICALS,	)	B2
6 INC.,	)	
	)	
7	)	
Patent Owner.	)	
8 _____	)	

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13 VIDEO-RECORDED DEPOSITION OF

14 JEFFREY V. RAVETCH, M.D., Ph.D.

15 New York, New York

16 Friday, February 23, 2024

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23 Reported Stenographically By:
PATRICIA A. BIDONDE
24 Registered Professional Reporter
Realtime Certified Reporter
25 JOB#: 8733

ALXN2104
IPR2023-01070

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2
3 February 23, 2024
8:16 a.m.
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6 Video-Recorded Deposition of
7 JEFFREY V. RAVETCH held at the offices
8 of Cooley LLP, 55 Hudson Yards, New
9 York, New York, before Patricia A.
10 Bidonde, Stenographer, Registered
11 Professional Reporter, Realtime
12 Certified Reporter, Certified eDepoze
13 Court Reporter, Notary Public of the
14 States of New York, New Jersey, and
15 Connecticut.
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1 A P P E A R A N C E S

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20 (Via Videoconference)

21

22

23

24

25

1 A P P E A R A N C E S (CONTINUED)
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2 P R O C E E D I N G S

3 - - -

4 THE VIDEOGRAPHER: We are now on

5 the record. The time is 8:16 a.m. on

6 February 23, 2024. Audio and video

7 recording will continue to take place

8 until all parties agree to go off the

9 record. Please note that microphones

10 are sensitive and may pick up whispering

11 and private conversations.

12 This is the video-recorded

13 deposition of Dr. Jeffrey Ravetch in the

14 matter of Samsung Bioepis Co., LTD.,

15 versus Alexion Pharmaceuticals, Inc.

16 This deposition is being held at Cooley

17 LLP, New York, New York.

18 My name is Christian Bidonde. I

19 am the legal video specialist. The

20 certified stenographer is Patricia

21 Bidonde on behalf of TransPerfect Legal

22 Solutions.

23 Counsel will state their

24 appearances for the record and all those

25 appearing remotely will be noted for the

1 record. Then the certified stenographer
2 will swear in the witness.
3 MR. COCHRAN: Andrew Cochran of
4 Cahill Gordon for Patent Owner, Alexion.
5 With me I have my colleague Andrew
6 Solomon also of Cahill Gordon, and on
7 the line we have Christine Hlavka from
8 Alexion.
9 MR. KNAUSS: Good morning. Dan
10 Knauss from Cooley for petitioner,
11 Samsung Bioepis.
12 J E F F R E Y R A V E T C H, called as a
13 witness, having been duly sworn by a
14 Notary Public, was examined and
15 testified as follows:
16 EXAMINATION BY
17 MR. COCHRAN:
18 Q. Good morning, Dr. Ravetch.
19 A. Good morning.
20 Q. Please go ahead and state your
21 full name for the record.
22 A. Jeffrey Ravetch.
23 Q. And are you currently employed?
24 A. Yes, I am.
25 Q. Where are you currently employed?

1 A. The Rockefeller University in New
2 York City.
3 Q. And where do you live?
4 A. I live in New York City as well.
5 Q. Okay. Have you ever had your
6 deposition taken before?
7 A. Yes, I have.
8 Q. How many times?
9 A. I don't keep a accurate record,
10 but probably starting 30 years ago, one or two
11 a year. So you can do the math.
12 Q. And were those patent
13 litigations?
14 A. Yes.
15 Q. All of them?
16 A. As far as I can recall,
17 patent-related, intellectual property-related
18 matters.
19 Q. Okay.
20 A. In the area of biotechnology.
21 Q. And do you recall if you've
22 always opined on the invalidity of patents?
23 A. No. I've opined on a variety of
24 topics related to patents as well as some of
25 the underlying technology. I've given

1 tutorials, for example, that were background
2 information. I've testified in claim
3 construction hearings as well earlier on. So
4 variety of different activities related to
5 patent matters.
6 Q. Okay. Excellent. So you --
7 assume you are aware of all of the ground
8 rules that us attorneys like to talk about
9 during the beginning of depositions?
10 A. I hope so, yes.
11 Q. And is there any reason why you
12 cannot give me truthful and accurate testimony
13 today?
14 A. There is not.
15 Q. Okay. So I am going to take less
16 breaks today, if possible. But if you need a
17 break at any time today, please do let me
18 know. And I think I do need to take a break
19 about every hour and a half -- right? -- to
20 switch the tapes? And that goes for everybody
21 in the room. I just want to be as efficient
22 as possible.
23 A. Okay.
24 Q. So I have already marked ten
25 exhibits. They are sitting here in front of

1 you. The first five are the patents.
2 Can you go ahead and please open
3 that first binder and take a look at each
4 exhibit, 1 through 5. And if you can, for me,
5 please, sir, confirm that those are the
6 patents that are at issue in these IPR?
7 (Ravetch Exhibit 1, US Patent
8 Number 9,732,149 B2, marked for
9 identification, as of this date.)
10 (Ravetch Exhibit 2, US Patent
11 Number 9,725,504 B2, marked for
12 identification, as of this date.)
13 (Ravetch Exhibit 3, US Patent
14 Number 9,718,880 B2, marked for
15 identification, as of this date.)
16 (Ravetch Exhibit 4, US Patent
17 Number 10,590,189 B2, marked for
18 identification, as of this date.)
19 (Ravetch Exhibit 5, US Patent
20 Number 10,703,809 B1, marked for
21 identification, as of this date.)
22 (Ravetch Exhibit 6, Ravetch
23 Declaration in Support of Petition in
24 IPR2023-00933, marked for
25 identification, as of this date.)

1 (Ravetch Exhibit 7, Ravetch
2 Declaration in Support of Petition in
3 IPR2023-00999, marked for
4 identification, as of this date.)
5 (Ravetch Exhibit 8, Ravetch
6 Declaration in Support of Petition in
7 IPR2023-00998, marked for
8 identification, as of this date.)
9 (Ravetch Exhibit 9, Ravetch
10 Declaration in Support of Petition in
11 IPR2023-01069, marked for
12 identification, as of this date.)
13 (Ravetch Exhibit 10, Ravetch
14 Declaration in Support of Petition in
15 IPR2023-01070, marked for
16 identification, as of this date.)
17 A. (Document review.)
18 Yes, they are.
19 BY MR. COCHRAN:
20 Q. You can set that to the side for
21 now and turn to the next binder, which I have
22 marked as Exhibits 6 through 10. And each of
23 these should be your declarations that you
24 submitted in these IPRs?
25 If you could please take a look

1 through them and confirm that they are your
2 declarations.
3 A. (Document review.)
4 They appear to be, yes.
5 Q. Okay. Great. Just a few
6 housekeeping things.
7 Would you agree that each of the
8 five declarations you submitted in these IPRs
9 are relatively similar to each other?
10 A. Each declaration addresses the
11 particular issues related to the patents that
12 I'm opining on. There are some overlaps
13 between them but they are all distinctive.
14 Q. Okay. I might be referring to
15 just a single one of them today for ease.
16 If we are having a discussion on
17 something and you know that there is something
18 more specific in another one of your
19 declarations, can you point me to it, please?
20 A. Yes, of course.
21 Q. Thank you very much.
22 And if you could please confirm
23 for me that you signed all five declarations?
24 A. I did confirm that, yes.
25 Q. Okay. And please turn to your

1 CV, which is attached as Exhibit A to each of
2 your declarations.
3 A. Yes, I have it.
4 Q. Thank you.
5 Can you confirm for me that this
6 is a fair and accurate summary of your
7 employment and education history?
8 A. It is until about, I would say,
9 six months ago. The publication list has
10 grown a bit since I submitted these.
11 Q. Okay. What have you written
12 about in the past six months?
13 A. Same general topics: antibody
14 therapeutics, the various mechanisms by which
15 they act in vivo, and various considerations
16 about antibody structure and function.
17 Q. Okay. Dr. Ravetch, is there
18 anything that you would like to correct in any
19 of your declarations sitting here today?
20 A. Not that I'm aware of as I sit
21 here now.
22 Q. Is there anything that you would
23 like to add to any of your declarations,
24 sitting here today?
25 A. Again, not that I'm aware of,

1 sitting here now.
2 Q. So you're not holding anything
3 back on us -- right? -- to spring on us at a
4 later time? Everything -- I'm sorry, go
5 ahead.
6 MR. KNAUSS: Object to the form.
7 A. I reserve the right to respond to
8 other opinions that are offered in this case.
9 So there may be additional documents or
10 comments that I make as this matter develops.
11 But as we sit here today, given
12 the instructions I was provided to review,
13 these are complete documents.
14 Q. Okay. Good. Thank you very
15 much.
16 Dr. Ravetch, how did you know
17 that Sequence ID Number 2 in the challenged
18 patents was a hybrid IgG2/G4 amino acid
19 sequence?
20 MR. KNAUSS: Object to the form.
21 A. So are you referring to any
22 particular declaration or in general?
23 Q. I'm referring to the patents,
24 Sequence 2 in the patents?
25 A. Sequence 2 in the patents?

1 Q. Yup.
2 A. So you're asking -- I'm not sure
3 I understand the question. How did I know the
4 sequences in the patents had hybrid G2/G4 Fc
5 domains, is that the question?
6 Q. That's the question.
7 A. Right. So I think that relates
8 more to an analysis that I performed to
9 understand what a POSA, in 2007, would
10 understand the structure of the eculizumab
11 antibody would have been.
12 And in my analysis of that
13 structure, I was able to ascertain that
14 eculizumab, as of 2007, was known to be a
15 hybrid G2/G4 molecule. With that information,
16 I was then able to compare it to the actual
17 sequence information found in the patents for
18 Sequence ID 2 and 4 and confirm that the same
19 material was found.
20 Q. So no one told you that the
21 Sequence Number 2 in the patents was a hybrid
22 sequence. Right?
23 A. No one directed my efforts. I
24 worked independently on this.
25 Q. Okay. And you cite a number of

1 references in your declaration and rely on
2 several of them for alleging that the patents
3 are invalid. Right?
4 A. I specifically performed an
5 analysis to look at anticipation in one patent
6 case, the '149 patent, and obviousness in the
7 other patent.
8 And there were various grounds
9 that I established based on the prior art that
10 established that those patents -- the claims
11 in those patents were obvious based on the
12 prior art that I analyzed.
13 Q. Do you recall which of the prior
14 art that you relied on actually mentioned the
15 word "eculizumab"?
16 A. Eculizumab. Okay. So --
17 MR. KNAUSS: Object to the
18 question. I think it's overbroad.
19 But do your best.
20 A. Right. So I'll use the '149
21 declaration as an example of the analysis that
22 I carried out. For example, on page 59 when I
23 describe in general the findings in the Bell
24 patent application, which was published on
25 September 1, 2005, Bell explicitly discloses

1 an antibody called h5G1.1 carried the trade
2 name eculizumab. So that's one example of
3 where the prior art identified a particular
4 antibody, an antibody sequence to eculizumab.
5 And then on page 61 of my '149
6 declaration, under the Tacken reference, which
7 was a journal article published August 15,
8 2005, it says that he discloses an isotype
9 control antibody, h5G1.1-mAb (eculizumab);
10 Alexion Pharmaceuticals, "that contains 'the
11 same IgG2/G4 constant region' and 'is specific
12 for the human terminal complement protein
13 C5.'"
14 So those are two examples I found
15 in the prior art where there is direct
16 reference to eculizumab and a particular
17 antibody clone that was developed by Alexion.
18 Q. And you mentioned Bell.
19 A. Yes.
20 Q. Do you recall if Bell discloses a
21 sequence, an amino acid sequence?
22 A. (Document review.)
23 So we can look at the Bell
24 reference, but in my report on page 71 of the
25 '149 declaration, I discuss what Bell teaches

1 related to eculizumab. And as I said, it's
2 the human 5G1.1-mAb, and then Bell goes on to
3 say in paragraph 114 of my declaration:
4 "'Methods for the preparation of
5 human 5G1.1-mAb, human 5G1.1-scFv, and
6 other functional fragments of human
7 h5G1.1 are described in' Evans and
8 Thomas, 'the disclosures of which are
9 incorporated in their entirety.'"
10 So Bell refers us to the Evans
11 Patent application, and the Evans application
12 lists a variety of sequences for the variable
13 domains of eculizumab as well as other related
14 molecules.
15 Q. Okay. That's fair. But Bell
16 itself does not have an amino acid sequence --
17 A. Well, incorporated -- excuse me.
18 I didn't mean to talk over you.
19 Q. Within its four corners -- no
20 problem.
21 Within its four corners, Bell
22 itself does not disclose an amino acid
23 sequence. Right?
24 A. I've been informed by counsel
25 that, when a reference is incorporated in its

1 entirety into an application, it's as if all
2 the material from that application is in the
3 Patent itself. So by that definition, the
4 sequences of Evans are in Bell.
5 Q. Okay. We'll come back to those
6 two.
7 Dr. Ravetch, are you able to
8 identify an antibody from looking at the
9 sequence alone?
10 MR. KNAUSS: Object to form.
11 A. That's a very broad question,
12 Counsel. Do you have a particular antibody in
13 mind? There are literally 10 to the 12th
14 antibody sequences in nature. So it's not
15 a ...
16 MR. COCHRAN: I'd like to mark
17 as -- this as Exhibit 11.
18 (Ravetch Exhibit 11, Commercial
19 antibody sequence, marked for
20 identification, as of this date.)
21 Q. I can represent to you that this
22 is a commercial antibody, and can you identify
23 it?
24 A. Well, as --
25 MR. KNAUSS: Object to the form.

1 You may answer it, Dr. Ravetch.
2 A. As a scientist, you know, when
3 presented with a sequence, what we do
4 routinely is to run that sequence through a
5 database. There are a variety of databases.
6 For antibodies in particular,
7 there is a very useful collection of databases
8 that were compiled by the Antibody Society,
9 which is one that I use regularly.
10 And in doing so, it would provide
11 alignments for the sequences that would
12 instruct you as to the parts of the sequence
13 that relate to various antibodies, those that
14 are in the germ-line configuration, those that
15 have undergone somatic hypermutation and class
16 switching, as well as sequences that may have
17 been disclosed commercially as actual
18 products.
19 So that would be where I would
20 start my analysis. And that would inform me
21 if it's a commercial product that had been
22 disclosed, then it would identify it. If it
23 wasn't a disclosed commercial product but it
24 had elements that could be recognized for the
25 variable domains, the constant domains, the

1 CDRs, all of that is well within the skill of
2 a POSA.
3 Q. Okay. Great. Thank you. And
4 just so -- for the record, you cannot identify
5 this amino acid sequence just by looking at
6 it. Right?
7 MR. KNAUSS: Object to the form.
8 A. As a scientist, I wouldn't, you
9 know, presume to look at a sequence and want
10 to jump to any conclusions. That's why we
11 carry out analyses in a careful manner.
12 Q. Right. There's additional steps
13 that you would have to take to figure out what
14 the sequence is and what it contains. Right?
15 MR. KNAUSS: Object to the form.
16 A. Yeah, I wouldn't call them
17 additional steps. It is the routine step that
18 every scientist would perform. When given
19 something like this to analyze, you know,
20 depending upon the level of experience one
21 might have, you might recognize elements off
22 the top of your head, which I can do in some
23 of these cases.
24 But the bottom line is you would
25 rely upon the literature, which can be

1 compiled in databases.
2 Q. And one last question, can you
3 recognize what isotype this antibody has?
4 A. So once again, that's a simple
5 matter of analysis. The sequences of isotypes
6 go back to studies that I performed myself for
7 human isotypes back in the late, '70s and I
8 published them back in the late '70s for the
9 human IgG and IgA isotypes.
10 So that would be something that
11 would be in the database, easily accessible.
12 And I -- certainly, even after sequencing
13 those isotypes and publishing them, I didn't
14 memorize them. So I, of course, would rely
15 upon my own data to determine exactly what the
16 isotypes were.
17 Q. Okay. Thank you. You can put
18 that to the side. Thank you.
19 All right. Let's turn to the
20 patents. We can start with the '149 patent.
21 A. Yes.
22 Q. Actually, maybe I can shortcut
23 this a little bit. Can you -- I'm focusing in
24 on the claims of each of the five patents.
25 And I'd like to you confirm for me, please,

1 that each requires an antibody with Sequence
2 ID Number 2 and Number 4. And please take
3 your time to do that.
4 A. '149 has a single claim and it
5 reads:
6 "An antibody that binds C5
7 comprising a heavy chain consisting of
8 SEQ ID Number 2 and a light chain
9 consisting of SEQ ID Number 4."
10 The '504 patent has ten claims.
11 The first claim is:
12 "A method of treating a patient
13 suffering from paroxysmal nocturnal
14 hemoglobinuria (PNH) comprising
15 administering to the patient a
16 pharmaceutical composition comprising an
17 antibody that binds C5, wherein the
18 antibody comprises a heavy chain
19 consisting of SEQ ID Number 2 and a
20 light chain consisting of SEQ ID
21 Number 4."
22 Q. Okay.
23 A. It then lists an additional
24 series of claims that all refer to the method
25 of Claim 1. So it refers to the same SEQ ID 2

1 and 4. So I believe all of these claims
2 depend upon the claim that has the sequence
3 information SEQ ID 2 and 4.
4 Q. And I'm very happy you actually
5 said the name of PNH so I don't have to.
6 A. Thank you. The '880 patent has
7 three claims.
8 The first claim:
9 "A pharmaceutical composition for
10 use in treating a patient afflicted with
11 paroxysmal nocturnal hemoglobinuria
12 (PNH), wherein the composition is a
13 sterile, preservative free, 300 mg
14 single-use dosage form comprising 30 mls
15 of a 10 mg/ml antibody solution,"
16 wherein the antibody comprises a heavy
17 chain consisting of SEQ ID Number 2 and
18 a light chain consisting of SEQ ID
19 Number 4.
20 Claim 2:
21 "Is a pharmaceutical composition
22 comprising an anti-C5 antibody, wherein
23 the anti-C5 antibody comprises a heavy
24 chain consisting of SEQ ID Number 2 and
25 a light chain consisting of SEQ ID

1 Number 4."
2 And Claim 3 depends upon Claim 2,
3 thereby it has the same sequence
4 requirements.
5 Q. Okay. Let's move on to the next
6 one. The '189.
7 A. The '189 Patent has 8 claims.
8 The first claim is:
9 "A method of treating a patient
10 suffering from paroxysmal nocturnal
11 hemoglobinuria (PNH) comprising
12 administering to the patient a
13 pharmaceutical composition comprising an
14 antibody that binds C5, wherein the
15 antibody comprises a heavy chain
16 consisting of SEQ ID Number 2 and a
17 light chain consisting of SEQ ID
18 Number 4, and wherein the composition
19 comprises a single-unit dosage form
20 comprising 300 milligrams of the
21 antibody and 30 ml of a sterile,
22 preservative-free solution."
23 Q. Okay. And let's go to the last
24 one, the '809 Patent?
25 A. Well, I mean, Claim 5 is also an

1 independent claim in this Patent.
2 Q. Sorry.
3 A. Claims 2, 3, and 4, depend upon
4 Claim 1. Claim 5 is an independent claim that
5 calls out SEQ ID 2 and 4. It reads:
6 "A method of treating a patient
7 suffering from paroxysmal nocturnal
8 hemoglobinuria (PNH) comprising
9 administering to the patient a
10 pharmaceutical composition comprising an
11 antibody that binds C5, wherein the
12 antibody comprises a heavy chain
13 consisting of SEQ ID Number 2 and a
14 light chain consisting of SEQ ID Number
15 4, wherein the composition comprises a
16 single-unit dosage form comprising 300
17 milligrams of the antibody in 30 ml of a
18 sterile, preservative-free solution, and
19 wherein the patient exhibits decreased
20 lactate dehydrogenase levels."
21 And then the next three claims,
22 6, 7, and 8 depend upon Claim 5 as well.
23 Q. All right. Thank you.
24 A. And finally the '809 Patent lists
25 29 claims. The first claim:

1 "A method of treating a patient
2 having paroxysmal nocturnal
3 hemoglobinuria (PNH), wherein the method
4 comprises intravenously administering to
5 the patient an antibody that binds C5,
6 wherein the antibody comprises a heavy
7 chain consisting of SEQ ID Number 2 and
8 a light chain consisting of SEQ ID
9 Number 4."
10 And best I can tell, the rest of
11 the claims are depending upon Claim 1,
12 and therefore, include the limitation of
13 SEQ ID 2 and 4 as well.
14 Q. All right. Thank you. I
15 appreciate that. So if I were to generalize
16 the five patents, each Patent claims a
17 specific antibody. Right?
18 A. Well, they claim method of
19 treatment, they claim compositions, they claim
20 in the '149 case simply the antibody itself,
21 and it defines the antibody by two sequences,
22 SEQ ID 2 and 4.
23 Q. Okay. But they all, all the
24 patents include the elements of the Sequence
25 ID Numbers 2 and 4. Right?

1 A. They all include the limitations
2 of SEQ ID's 2 and 4.
3 Q. Okay. All right.
4 A. That's how I understand it.
5 Q. And the antibody described in
6 Sequence ID 2 and 4 is an antihuman C5
7 antibody. Right?
8 A. (Document review.)
9 Q. I'll actually strike that
10 question and ask it a little differently.
11 The antibody described in
12 Sequence ID Numbers 2 and 4 is an anti-C5
13 antibody. Right?
14 A. (Document review.)
15 So on Column 30 under
16 "Sequences," it lists eculizumab heavy chain
17 SEQ ID Number 2 and SEQ ID Number 4 is
18 eculizumab light chain. So that's the
19 description provided in the Patent for those
20 two sequences.
21 Q. So you don't know if that is an
22 anti-C5 antibody?
23 A. Eculizumab, as I stated earlier,
24 has been defined as an antibody that binds C5
25 and inhibits the conversion of C5 to C5a and

1 b. That was known in the prior art.
2 Q. All right. Switch back to your
3 declaration. And I'll be referring to the
4 '880 declaration which is Tab 3 in this
5 binder, but again, if there's anything that
6 we're discussing that you'd like to point me
7 to that's missing from the '880 declaration
8 and in another declaration, please let me
9 know.
10 If you can please go to paragraph
11 16 which is on page 18.
12 A. Yes.
13 Q. This is where you discuss a
14 person of ordinary skill in the art. Right?
15 A. That is correct.
16 Q. And then in paragraph 16, the
17 second sentence starting with "For purposes."
18 Do you see that?
19 A. Page 18 paragraph 16?
20 Q. Yeah. "For purposes of the '880
21 Patent"?
22 A. What am I doing here wrong here?
23 (Document review.)
24 Yes, I'm sorry. It's second full
25 sentence, I'm sorry. I was looking at the

1 second line. My apologies.
2 Q. So in this sentence you say:
3 "I have assumed that the date of
4 the patents is March 15, 2007, which is
5 the date the earliest application in the
6 Patent family from which the '880 Patent
7 issued."
8 Right?
9 A. "Was filed," that's what I state,
10 yes.
11 Q. "Was filed."
12 So you agree that the earliest
13 priority date of the '880 Patent is March 15,
14 2007?
15 A. That's my understanding. The
16 next sentence states that:
17 "I am not aware of any claim by
18 the Patent owner that the claims of the
19 '880 Patent are entitled to an earlier
20 date of invention, but I reserve the
21 right to supplement this opinion if the
22 Patent owner were to later claim that
23 the '880 Patent was entitled to an
24 earlier priority date."
25 So as of now, when I wrote this

1 declaration, that was the information that I
2 had in front of me.
3 Q. Understood. Is it your
4 understanding that March 15, 2007, is the
5 earliest priority date of all five of the
6 patents at issue here?
7 A. I'd have to look at each
8 declaration. But that's my general
9 understanding. It should be easy to
10 ascertain.
11 Q. Sure.
12 A. For the '504, March 15, 2-7, and
13 7 --
14 MR. KNAUSS: Did you say 2007,
15 Doctor?
16 THE WITNESS: 2007. Yes, I'm
17 sorry. Did I misspeak? Probably.
18 A. (Document review.)
19 For the '149, the date is
20 March 15, 2007.
21 (Document review.)
22 For the '189, March 15, 2007,
23 I've stated. And for the '809, March 15,
24 2007.
25 Q. Thank you, sir.

1 And you performed your analysis
2 regarding the validity of the five patents at
3 issue here based on that date. Right?
4 A. That's correct.
5 Q. And you understand that March 15,
6 2007, is the priority date being used in this
7 case for assessing the state of the art at the
8 time?
9 A. That's correct.
10 Q. And do you understand that the
11 anticipation and obviousness grounds at issue
12 in these proceedings are to be assessed from
13 the perspective of a person of ordinary skill
14 in the art as of that date?
15 A. That's my understanding, yes.
16 Q. If I use the abbreviation today
17 of a "POSA," would you understand that?
18 A. Yes, I would.
19 Q. So each of your declarations
20 provides a definition of a POSA. Right?
21 A. That's correct.
22 Q. And that definition is included
23 in, for example, paragraph 19 of the
24 declaration you submitted for the '880 Patent.
25 Right?

1 A. (Document review.)
2 Yes, I provide a definition in
3 the '880 Patent.
4 Q. And that's the definition you
5 relied on in this case?
6 A. That's the definition that I have
7 relied upon, yes.
8 Q. The very last sentence of
9 paragraph 19 says "a POSA could have also
10 worked as part of a multidisciplinary team."
11 Right?
12 A. Yes.
13 Q. So does that mean a POSA wouldn't
14 be able to do this alone?
15 MR. KNAUSS: Object to the form.
16 You may answer.
17 A. Now, there are alternative ways
18 to understanding the knowledge that a POSA
19 would possess. And it's my understanding
20 that, in addition to the criteria that I laid
21 out in paragraph 17, for example, a POSA could
22 also have worked as part of a team and drawn
23 upon, not only his or her own skills, but upon
24 specialized skills of team members.
25 And I list, for example, a

1 clinician, a doctor of pharmacy, and a
2 formulation chemist who are part of a team to
3 help solve a given problem.
4 Q. All right. So if there was a
5 problem of determining an amino acid sequence,
6 you would need to draw upon multiple
7 individuals to help figure it out?
8 A. Not necessarily. It depends upon
9 the nature of the problem, what the given
10 problem is, as I state in my definition.
11 So if it's an issue related to
12 the amino acid sequence, a POSA with the
13 background that I specify would be able to
14 determine the components of that sequence, for
15 example. But for other problems, the use of a
16 team of individuals may, in fact, be
17 appropriate.
18 Q. The definition you provide in
19 paragraph 19, is that the same in all five of
20 your declarations?
21 A. As far as I recall, that seems to
22 be the case. Once again, I would want to
23 confirm that that's the case.
24 Q. Feel free to do so, if you want
25 to.

1 A. (Document review.)
2 Yes, they all appear to be the
3 same.
4 Q. Thank you.
5 A. In that paragraph, yes.
6 Q. So according to you, and choose
7 your paragraph of liking -- or declaration of
8 liking, paragraph 19 in the '880 declaration,
9 definition of a POSA, according to you, it's
10 your opinion that the level of ordinary skill
11 in the relevant art is high. Right?
12 A. Was high as of 2007.
13 Q. Was high.
14 Why?
15 A. The field of antibody engineering
16 and antibody treatment for a variety of
17 diseases was 20 years-plus well developed. So
18 the -- or 30 years.
19 As I said, the first antibodies
20 were cloned back in the '70s. By the '80s,
21 therapeutic antibodies were being developed.
22 Humanization technologies had been presented
23 by Winter and his colleagues. Therapeutic
24 antibodies entered into clinical practice by
25 the '90s.

1 So by 2007, we had about 30 years
2 of expertise had accumulated in this field to
3 understand the nature of antibodies, how they
4 could be used, manipulated, and deployed as
5 therapeutics in a variety of indications,
6 including inflammatory diseases, infectious
7 diseases, and neoplastic diseases.
8 Q. The next sentence, paragraph 19
9 of your '880 declaration says:
10 Specifically a POSA, as of
11 March 2007, "would have knowledge of the
12 scientific literature and have skills
13 relating to the design and generation of
14 antibodies, the complement system, and
15 the application of antibodies as
16 therapeutics before March 15, 2007."
17 Do you see that?
18 A. Yes, I do.
19 Q. Why is the design and generation
20 of antibodies pertinent to the field of the
21 challenged patents?
22 A. The challenged patents refer to a
23 particular antibody, eculizumab, for -- in
24 some of the patents, in some of the claims,
25 for its use in the treatment of a disease,

1 PNH, as we discussed, using specific routes of
2 administration, formulations, concentrations.
3 So all of that is included in the
4 understanding of a POSA as of 2007 because of
5 all the information that had been developed in
6 the field by others working in similar
7 technologies.
8 Q. Why is the complement system
9 pertinent to the challenged patents?
10 A. Right. So it was known by 2007
11 that antibodies have the ability to activate
12 the complement cascade, that's one aspect, and
13 that antibodies can be deployed as
14 therapeutics to inhibit complement activation.
15 And eculizumab specifically is an
16 antibody that was developed for the express
17 purpose of inhibiting a particular component
18 of the complement activation pathway.
19 The complement pathway had been
20 known for many years prior to 2007. It goes
21 back to the '50s, actually, when it was first
22 described. Actually, to be fair, it goes back
23 to Ehrlich in 1903.
24 But, you know, so we have 100
25 years of expertise in understanding the

1 complement cascade and the biochemistry behind
2 complement. And in particular, its role in
3 particular diseases like PNH was well defined.
4 So it is a matter of a POSA to
5 have that expertise when examining an antibody
6 whose purpose is to inhibit complement
7 activation of a particular component of the
8 cascade.
9 Q. You mentioned that antibodies
10 have the ability to activate the complement
11 cascade?
12 A. Right. So --
13 Q. How do they do that?
14 A. I'm sorry.
15 MR. KNAUSS: Just wait for the
16 question.
17 THE WITNESS: I'm sorry. Yes.
18 Q. How do they do that?
19 A. How do antibodies do that?
20 Q. How do they do that?
21 A. Right. So how much time do you
22 have, Counselor?
23 Q. All day.
24 A. Okay. Because this is an area
25 that I've spent my career studying, quite

1 frankly.
2 So depending upon the isotype of
3 the antibody, they can activate the complement
4 cascade directly or they can activate the
5 complement cascade indirectly.
6 IgM, for example, will directly
7 activate the complement cascade through
8 interaction with early components called the
9 C1q pathway. IgG antibodies, while in vitro
10 having the capacity to activate a C1q pathway,
11 in vivo rely much less upon the classical
12 complement activation through C1q and,
13 instead, activate the complement cascade
14 through other intermediates like the Fc
15 receptor family.
16 In the paper I published back in
17 the mid-'90s, studying a reaction called the
18 Arthus reaction, we indicated that the immune
19 complex activation, which leads to terminal
20 complement deposition is actually initiated by
21 Fc receptors. And that was a key
22 understanding of the distinction between
23 classical complement activation and the
24 mechanism by which antibodies of the IgG class
25 were able to influence complement activation.

1 Be that as it may, we've known
2 for many years that you can demonstrate
3 engagement of complement components with IgG
4 subclasses, and different subclasses had
5 different capacities to engage the complement
6 cascade and Fc receptors.
7 So in the consideration that one
8 would have in developing an antibody
9 therapeutic, there are times when you want to
10 optimize engagement of the Fc receptor
11 pathway, and subsequently the complement
12 pathway, and there are times when you want to
13 limit the engagement of the activating
14 receptors and the complement cascade. And all
15 of that information was well-known prior to
16 2007.
17 Q. What are some of the reasons why
18 you might want to limit the engagement of the
19 Fc receptor for a therapeutic antibody?
20 A. So if one is developing a
21 therapeutic antibody for an inflammatory
22 disease, PNH being an example of a cytotoxic
23 pathway, antibodies that are involved in the
24 therapeutic intervention in arthritis,
25 autoimmune diseases, for example, those are

1 examples where you're trying to limit the
2 activation of inflammatory pathways, and those
3 antibodies traditionally are designed through
4 a variety of mechanisms to minimize their
5 engagement with Fc receptors.
6 In contrast, if you're developing
7 a therapeutic antibody for the treatment of
8 neoplastic diseases, for cancers, for tumors,
9 or for infectious diseases, you want to
10 activate the Fc receptor pathway quite
11 specifically to help eliminate those
12 challenges, be they transformed cells or
13 infected cells by viruses, for example.
14 Q. And a similar question, in what
15 ways -- strike that question.
16 What are some of the reasons why
17 you may want to limit the engagement of
18 complement for a therapeutic antibody?
19 A. Right. Well, as I said, let's
20 take the example of a disease like PNH, which
21 is the inappropriate activation of the
22 terminal complement pathways by virtue of the
23 loss of specific complement suppressing
24 pathways on various cells. Those cells have
25 mechanisms to protect them from inappropriate

1 activation of complement.
2 PNH is a genetic disorder where
3 you lose that capacity on certain cells, like
4 red blood cells and platelets. Developing a
5 therapeutic that would activate complement
6 would undermine the very purpose of your
7 therapeutic. So, of course, you want to have
8 a therapeutic that is developed to minimize
9 complement activation and Fc receptor
10 activation.
11 And the same argument goes if you
12 want to use an antibody for the treatment of
13 an autoimmune disease, like hemolytic anemia
14 or thrombocytopenia. You also don't want to
15 enhance the ability to destroy those cells.
16 You're trying to preserve those cells.
17 Q. Okay. Going back to paragraph
18 19 --
19 A. Yes.
20 Q. -- of your '880 declaration. You
21 also mention that a POSA would have the
22 knowledge of the application of antibodies as
23 therapeutics. Right?
24 A. Correct.
25 Q. So why is that pertinent to your

1 definition of a POSA?
2 A. Right. Because developing
3 antibodies as therapeutic entities involves
4 the appreciation of the properties that
5 antibodies have, you know, in the body. So
6 those are in vivo studies as opposed to simply
7 what happens in the test tube, which are in
8 vitro studies.
9 So to develop a therapeutic
10 antibody, in vivo studies are frequently
11 required to illustrate the particular
12 properties antibodies would have when they're
13 introduced into a complex organism.
14 And that includes things like
15 half-life of the antibody, bioavailability of
16 the antibody, its stability in the body as
17 opposed to stability outside the body.
18 So those are all additional
19 considerations that do not necessarily get
20 revealed in a simple test tube study --
21 right? -- so that's an additional aspect.
22 And that was, once again, also
23 well-known by 2007, because we had, once
24 again, close to 20 years of expertise in the
25 application of antibodies as therapeutic

1 entities, everything from their purification
2 to their formulation to their concentration,
3 their stability, their pharmacodynamics, and
4 their pharmacokinetics had been developed for
5 a number of antibodies by that point.
6 Q. So by that point, developing a
7 therapeutic antibody was relatively easy?
8 A. I didn't say that, Counselor. I
9 said that the steps that were required were
10 known to one of skill in the art. And that's
11 where having a team is often required in
12 moving from simply generating the monoclonal
13 antibody by the well-established techniques of
14 Kohler and Millstein, for example, or the
15 screening of combinatorial libraries using the
16 Winter techniques, going to a therapeutic
17 formulation for the treatment of disease.
18 All those steps were developed
19 but require expertise that's not beyond the
20 ability of one of skill in the art in 2007.
21 And one would have a reasonable expectation of
22 success given all that was known before.
23 Q. Dr. Ravetch, why is half-life
24 important for a therapeutic antibody?
25 A. Right, so --

1 MR. KNAUSS: Object to the form.
2 You may answer.
3 A. Yeah, so half-life refers to the
4 duration of an antibody's presence in a
5 biological system, like an animal or a human
6 or a macaque, for that matter. And it
7 determines the frequency of treatment.
8 In some cases, you want
9 antibodies with short half-lives where you
10 don't want the antibody to persist. Some of
11 the earliest antibodies were developed for the
12 treatment of myocardial infarction. You want
13 a very short half-life to simply impact on the
14 acute event.
15 In other cases, you want to have
16 a dosing schedule, which is more extended,
17 where you dose once a month or once every two
18 weeks or once every six months, and half-life
19 determines things like that, because the
20 critical concentration an antibody has to
21 achieve, based on the route of administration,
22 will determine its ultimate biological
23 properties and efficacy.
24 Q. Okay. Does every antibody have
25 the same half-life?

1 A. So different subclasses will have
2 different -- sorry -- different isotypes will
3 have different half-lives. Right? So IgM has
4 a different half-life than IgG or IgA or IgE.
5 Half-life is determined by a
6 variety of factors, and it's well-known that
7 the pathways that determine antibody half-life
8 involve a particular receptor called the FcRn,
9 or the neonatal receptor, which is also
10 involved in transepithelial transport.
11 So FcRn binding is a criteria
12 that we use. That is one component of the
13 half-life consideration. It's a critical one.
14 In the absence of FcRn, an antibody's
15 half-life, which typically is about two weeks
16 in the human, will reduce to several hours.
17 But that doesn't mean that every
18 antibody with FcRn binding activity has a
19 two-week half-life. Other considerations
20 apply, and there is a range of half-lives that
21 have been observed for different antibodies.
22 Q. And for any given antibody, if
23 you were to change the amino acid sequence,
24 would that affect the half-life of the
25 antibody?

1 MR. KNAUSS: Object to the form.
2 You may answer.
3 A. Right. So once again, we know
4 precisely where FcRn engagement occurs. We
5 know precisely how FcRn protects antibodies
6 from the degradation that would occur upon
7 internalization and lysosomal degradation.
8 So if you're making amino acid
9 substitutions in the FcRn binding side of the
10 antibody, we have predictable outcomes for
11 what would happen to the antibody.
12 Amino acid substitutions outside
13 the FcRn binding pocket do not have impact on
14 half-life in general, but the assays that one
15 would do are quite routine, and it's easy to
16 determine if your antibody is going to have an
17 affect on its half-life by making
18 substitutions in the Fc domain.
19 Q. You mentioned you have
20 predictable outcomes. Right?
21 A. That's correct.
22 Q. Not guaranteed outcomes. Right?
23 A. Well, you have a reasonable
24 expectation of success for what would happen
25 if you make particular changes. That's

1 correct.
2 Q. And when you refer to "we know
3 precisely" --
4 A. Yes.
5 Q. -- what are you relying on for
6 that?
7 A. Crystal structure analysis. We
8 know the contact sites between FcRn and IgG
9 antibodies. Those crystal structures have
10 been solved and we can precisely map which
11 amino acids make contact between the IgG and
12 the FcRn to determine its ability to be
13 internalized and not -- and recycled as
14 opposed to degraded -- right? -- and those are
15 pH-sensitive residues on the Fc domain.
16 Q. Do you know when those crystal
17 structures were analyzed?
18 A. I'd have to review, you know, the
19 literature. I did not address that issue in
20 this report, but I believe that was in the
21 early 2000s by Dr. Bjorkman and her
22 colleagues, but that would be something to
23 determine.
24 FcRn pathways were actually known
25 in the '80s, but the actually contact sites

1 were determined somewhat later by crystal
2 studies. There were mutational studies that
3 were done in the '90s that define some of
4 those interactions.
5 But I think if you ask for a
6 definitive structural analysis, that was done
7 by the crystal structure of Bjorkman and
8 colleagues.
9 MR. COCHRAN: Yeah, let's go
10 ahead and take a break.
11 THE VIDEOGRAPHER: The time is
12 9:19 a.m. This concludes Media 1. Off
13 the record.
14 (Recess taken from 9:19 a.m. to
15 9:33 a.m.)
16 THE VIDEOGRAPHER: The time now
17 is 9:33 a.m. This begins Media 2. On
18 the record.
19 (Ravetch Exhibit 12, Declaration
20 of Arturo Casadevall for Patent Number
21 9,732,149 B2, marked for identification,
22 as of this date.)
23 (Ravetch Exhibit 13, Declaration
24 of Arturo Casadevall for Patent Number
25 9,725,504 B2, marked for identification,

1 as of this date.)
2 (Ravetch Exhibit 14, Declaration
3 of Arturo Casadevall for Patent Number
4 9,718,880 B2, marked for identification,
5 as of this date.)
6 (Ravetch Exhibit 15, Declaration
7 of Arturo Casadevall for Patent Number
8 10,590,189 B2, marked for
9 identification, as of this date.)
10 (Ravetch Exhibit 16, Declaration
11 of Arturo Casadevall for Patent Number
12 10,703,809 B1, marked for
13 identification, as of this date.)
14 By MR. COCHRAN:
15 Q. So I have marked as Exhibits 12
16 to 16 declarations from Dr. Arturo Casadevall.
17 Have you seen these declarations
18 before?
19 A. I believe I have, yes.
20 Q. Have you read them?
21 A. I've reviewed them.
22 Q. And you know Dr. Casadevall?
23 A. I do.
24 Q. And you guys are friendly with
25 each other?

1 A. We are colleagues, yes.
2 Q. Is he a good scientist?
3 A. Yes, he is.
4 Q. All right. If you can, please,
5 go to Dr. Casadevall's declaration for the
6 '149 patent, Tab 1.
7 A. Yes.
8 Q. And we're going to go to page 42.
9 All right. And as we go through these
10 questions, feel free to read anything that you
11 need to read in Dr. Casadevall's declaration.
12 But let's go to paragraph 104 on
13 page 42. And the second sentence starting
14 with "one particular."
15 It says:
16 "One particular complicating
17 factor was the inability to reasonably
18 predict the in vitro and in vivo
19 properties and effects of an untested
20 monoclonal antibody based only on its
21 primary amino acid sequence."
22 Right?
23 A. Yes.
24 Q. Do you agree with that sentence?
25 A. Well, it's a very broad sentence.

1 I wouldn't generalize in that way. It depends
2 on how one obtains the monoclonal antibody,
3 what your screening method was for obtaining
4 the antibody. That immediately tells you if
5 it's an antibody that binds to the epitope of
6 interest, if it has activities.
7 Many of the screens that we do
8 directly limit the antibodies that you study
9 to those that have the biological activity
10 you're looking for. So I think it's just an
11 overly broad statement.
12 Q. But you have no reason to
13 disagree with that statement. Right?
14 MR. KNAUSS: Object to the form.
15 A. As I said, I would not have made
16 a statement like that out of context. And,
17 you know, my declarations relate specifically
18 to the questions that I was asked to address,
19 which relate to the obviousness or
20 anticipation of the claims of the patents that
21 we've been discussing based on the prior art
22 of 2007.
23 Q. Lets go on to paragraph 105, on
24 to page 43, the last sentence of that
25 paragraph. This sentence says:

1 "But well before March 15, 2007,
2 a POSA in the field of the '149 patent
3 would have been attuned to an increasing
4 body of scientific literature showing
5 that the antibody binding (including
6 affinity and specificity) could be
7 impacted by amino acid changes outside
8 the CDR regions."
9 Do you see that?
10 A. Yes, I do.
11 Q. Do you agree with
12 Dr. Casadevall's sentence?
13 A. Right. So I think the next
14 paragraph he gives more detail about changes
15 to the framework regions. And that was work
16 that was first published by Greg Winter's
17 group.
18 In the humanization process, the
19 Riechmann publication is the one that is most
20 frequently cited, which provided the basis for
21 the understanding that the frameworks held the
22 CDRs in particular confirmations that
23 optimized their engagement with the antigenic
24 epitope.
25 So this is known, as he says, and

1 I agree. We knew that changes to the
2 framework were potentially important, not in
3 every case, but it was something that was
4 taken into account.
5 And by 2007, a wide number of
6 humanized antibodies had been developed. Some
7 with framework changes; some without framework
8 changes.
9 I should just note that
10 eculizumab, when framework changes were
11 introduced, had no impact on CDR-binding
12 specificity or affinity. So it is a
13 conclusion that we're all familiar with.
14 Q. Okay.
15 A. So it's not unpredictable. It's
16 easily testable.
17 Q. It's not unpredictable but it's
18 easily testable? Is that what --
19 A. So while you -- while looking at
20 a sequence is not the way people who study
21 antibodies analyze this art, the sequence is a
22 starting point from which you generate the
23 protein. And then simple biochemical assays
24 that are routine experimentation are done to
25 determine, you know, parameters like CDR

1 binding and framework requirements.
2 So you know, I would not ever
3 state that, you know, one looks at a sequence
4 and is confounded by what the sequence
5 provides, because we know exactly how to go
6 from that information to the biological
7 relevance of that information.
8 Q. But you agree that amino acid
9 changes outside the CDR regions could affect
10 antibody affinity. Right?
11 A. That had been published back in
12 the '80s, yes.
13 Q. And changes to amino acid
14 sequences outside the CDR regions could also
15 impact the specificity of the antibody too.
16 Right?
17 A. Well, once again, if you reduce
18 the binding of a particular point where you're
19 no longer getting reasonable affinity, you
20 begin to show nonspecific polyreactivity, so
21 that, of course, impacts on specificity.
22 But in general, as I said, by
23 2007, we've had 20 years of expertise and
24 experience in this area, knowing how to
25 engineer an antibody for humanization.

1 Q. And the impacts that are changed
2 to the amino acid sequence of an antibody
3 might have were not predictable. Right?
4 A. Once again, I'm not sure I
5 understand. Looking at the sequence itself is
6 not the way a POSA analyzes antibody structure
7 or function, you know.
8 It's a component, of course,
9 because you have to then express it, but, you
10 know, we do not have algorithms that will tell
11 us this amino acid will do this. But that's
12 irrelevant because we know exactly how to
13 design antibodies.
14 And, you know, my task in this
15 matter was to focus on the eculizumab antibody
16 and understand what was known by 2007 about
17 eculizumab and its structure. And that was
18 all well-known in the art.
19 Q. So your task in this case was to
20 build eculizumab until you got the sequence in
21 the patents. Right?
22 MR. KNAUSS: Misstates the
23 testimony.
24 You may answer, Dr. Ravetch.
25 A. No, my task was to look at the

1 literature by 2007, the published literature
2 by 2007 from the perspective of a POSA, which
3 we just described, and determine whether a
4 POSA would have understood what the structure
5 of eculizumab was, and then with that
6 information, compare it to the claims to
7 determine if, in fact, that is the claim
8 matter.
9 So the analysis is done
10 independently of the claims. It's done simply
11 from the perspective of a POSA and what's in
12 the published literature as of 2007.
13 Q. Let's go to paragraph 106 of
14 Dr. Casadevall's declaration.
15 A. Yes.
16 Q. This is on page 43, second
17 sentence:
18 "As discussed in Section VI.D.2
19 above, it was known that the transfer of
20 murine CDRs into human framework regions
21 would often reduce the specificity and
22 affinity of a humanized variable
23 antibody or fragment relative to a
24 parent mouse antibody."
25 Do you see that?

1 A. I see that, yes.
2 Q. And do you agree with
3 Dr. Casadevall?
4 A. (Document review.)
5 Q. I take it you are reading the
6 section he refers to?
7 A. Yes, I am.
8 (Document review.)
9 Okay. I've reviewed the
10 Section VI.D.2, and I can now discuss the
11 issue that you raise in this sentence.
12 I just note, first of all, that
13 Dr. Casadevall changes his terminology. He
14 says in paragraph 75 that CDR grafting could
15 have reduced specificity, and here in 106 he
16 said would reduce specificity. I think he
17 meant "could" in both cases.
18 So I would agree that, yeah, CDR
19 grafting was known to potentially have an
20 impact on antibody affinity primarily.
21 But once again, in the case of
22 eculizumab, based on the Bell reference of
23 2005, the concerns that are presented by
24 Dr. Casadevall, as a generalized statement,
25 don't apply to the eculizumab because it was

1 known that that antibody had been administered
2 to patients, had clinical efficacy, had a
3 safety signal that was acceptable, did not
4 result in antibody responses to the
5 therapeutic.
6 So we knew quite a bit more about
7 eculizumab than this generic discussion that
8 Dr. Casadevall is presenting.
9 Q. But you don't disagree with this
10 discussion that Dr. Casadevall is
11 presenting --
12 A. Well, I disagree with --
13 MR. KNAUSS: Object to the
14 form --
15 A. I disagree with the insistence
16 that nothing was known and everything required
17 clinical testing. I disagree with that
18 because much was known, and many studies could
19 be done and many antibodies had been developed
20 that then went on to clinical testing that
21 were quite successful.
22 So by 2007, there was a body of
23 successfully humanized antibodies that were in
24 the clinic, that had, in fact, been FDA
25 approved for a variety of indications. Some,

1 at least half dozen or so. I can refer to my
2 declaration for the exact number.
3 So it's a very different world
4 than what it was in the late '80s when one was
5 first starting this process. 20 years of
6 experience has had a significant impact.
7 So I would disagree that clinical
8 testing was required for every study before
9 you knew you had a product. That's a
10 different standard for therapeutic approval,
11 but not consistent with my experience.
12 Q. Are you aware of any antibody
13 that was FDA approved before March of 2007
14 that had a hybrid constant region?
15 A. By "hybrid" you're referring to
16 derived from more than one isotype or
17 subclass.
18 Q. Correct.
19 A. I don't believe I've reviewed the
20 literature for that particular issue. But
21 I -- sitting here today, I don't -- I can't
22 think of any.
23 As Dr. Casadevall points out, G1
24 and G4 were the dominant subclasses that were
25 used, and there was a lot of expertise in

1 using G1 and G4 as well as the variants of G1
2 and G4. Amino acid variants of G1 and G4, I
3 should say.
4 Q. And at the time, those G1 and G4
5 antibodies were not hybrid antibodies. Right?
6 MR. KNAUSS: Object to the form.
7 But answer.
8 A. As far as the approved antibodies
9 by 2007, I believe that's correct.
10 Q. Right. The first sentence of
11 paragraph 107 of Dr. Casadevall's declaration
12 states:
13 "A POSA as of March 15, 2007,
14 also would have known that changes
15 related to the constant regions --
16 whether combining constant region
17 sequences, or portions thereof, with
18 variable region sequences from other
19 antibodies or truncated antibody
20 derivatives (e.g., 'fragments' such as
21 Fab or scFv) or switching the type of
22 constant regions used in a full-length
23 antibody -- could impact antigen binding
24 and other properties of the original
25 antibody/fragment."

1 Right?
2 A. I see that sentence, yes.
3 Q. Do you have any reason to
4 disagree with Dr. Casadevall?
5 A. I -- once again, as a generalized
6 statement, I would disagree. I think it's an
7 exception rather than the rule. And in my
8 experience, I've never encountered that
9 phenomenon.
10 I know that Dr. Casadevall has
11 published on that phenomenon. And I suspect
12 it applies only to a very limited class of
13 epitopes that are repetitive carbohydrate
14 epitopes.
15 But for all the antibodies that
16 I've studied and all the antibodies that I've
17 reviewed in both my role as an advisor to
18 biotech companies and in knowing the
19 literature, switching the constant region
20 domain of the heavy chain or light chain has
21 not impacted on the binding specificity or
22 affinity of the original Fab domains.
23 Q. When you combine two different
24 isotypes --
25 A. Isotypes or subclasses?

1 Q. Isotypes.
2 MR. KNAUSS: Hold on.
3 Go ahead and ask the question.
4 A. Please ask the question. I'm
5 sorry.
6 Q. No problem. You can correct me
7 if I'm wrong. You're the expert.
8 When you combine two different
9 isotypes, say, G2 and G4.
10 A. Those aren't isotypes.
11 Q. Subtypes.
12 A. Thank you.
13 Q. You combined two different
14 subtypes, would that -- could that impact the
15 antibody specificity and affinity?
16 MR. KNAUSS: Object to the form.
17 You may answer.
18 A. So Mueller did that experiment
19 and compared what happened when he made a
20 hybrid between G2 and G4, compared to G4 alone
21 or G2 alone, and saw no differences in the
22 eculizumab binding affinity and its ability to
23 inhibit the binding to his particular target
24 sequence which was an integrin sequence.
25 So we have data so we don't have

1 to speculate as to what might happen. And in
2 that case, there was no impact. So I would
3 answer that the G2/G4, because of the high
4 similarity between those sequences, as pointed
5 out by Mueller, and the actual data we have
6 from the Mueller publication in PCT, you know,
7 we know that that did not change the
8 properties of the variable domain binding.
9 Q. And we'll get to Mueller in a
10 little bit. But other than Mueller, are you
11 aware of any other publications that tested a
12 G2/G4?
13 A. That was the only publication
14 that I reviewed and that was relevant to this
15 analysis.
16 Q. Did you look for any others?
17 A. I have. I don't recall seeing
18 anything else that was relevant.
19 MR. COCHRAN: You can put
20 Dr. Casadevall's declarations aside for
21 now.
22 This shall be Exhibit 17.
23 (Ravetch Exhibit 17, "Inhibition
24 of complement activity by humanized
25 anti-C5 antibody and single-chain Fv" by

1 Thomas et al., marked for
2 identification, as of this date.)
3 MR. COCHRAN: This is an article
4 by Thomas et al. titled "Inhibition of
5 complement activity by humanized anti-C
6 antibody and single-chain Fv."
7 BY MR. COCHRAN:
8 Q. Have you seen this document
9 before?
10 A. Yes, I have.
11 Q. Have you read it before?
12 A. Yes, I have.
13 Q. Did you rely on this document in
14 your declarations?
15 A. I cite to this document, but I
16 don't rely upon it. I rely upon the evidence,
17 the evidence of the document for the sequences
18 of the humanized antibody eculizumab.
19 Q. Why don't you rely on Thomas?
20 MR. KNAUSS: Object to the form.
21 You may answer.
22 A. In my analysis of the prior art,
23 the evidence was more directly applicable
24 because of the citation to a particular
25 sequence that was also cited in Mueller.

1 Q. So a POSA would have understood
2 that Thomas describes both a full-length
3 humanized anti-C5 antibody as well as a
4 single-chain Fv. Is that correct?
5 A. Yes, that is correct.
6 Q. Is a scFv, single-chain variable
7 fragment, different than a full-length
8 antibody?
9 A. It's certainly in a different
10 structure overall, and there are some sequence
11 differences that are introduced into the
12 single-chain Fv that are not found in the
13 full-length antibody.
14 So it has a different
15 three-dimensional structure. It will have
16 discernible differences.
17 Q. Looking at the abstract of
18 Thomas.
19 A. Yes.
20 Q. Second sentence:
21 "Recently a monoclonal antibody
22 (5G1.1) that recognizes the human
23 complement protein C5, has been shown to
24 effectively block C5 cleavage, thereby
25 preventing the generation of the

1 proinflammatory complement components
2 C5a and C5b-9."
3 Do you see that?
4 A. I do.
5 Q. And that 5G1.1 is referring to
6 the mouse antibody. Right?
7 A. Well, the terminology is a bit
8 inconsistent. Many cases, a small "m" is
9 placed before the 5G1.1 to indicate it's
10 mouse. A small "h" is used to indicate that
11 it's humanized.
12 But I've seen examples in the
13 literature where that terminology is not
14 always applied. Nonetheless, it's easy to
15 recognize if the sequence that is being
16 discussed is a murine sequence or a humanized
17 sequence.
18 Q. How is it easy to recognize?
19 A. By, once again, comparing it to
20 the database of antibody sequences, and one
21 can identify framework regions that are either
22 human or mouse.
23 Q. Do you know what 5G1.1, what
24 specific sequence 5G1.1 is referring to in
25 Thomas here?

1 A. Well, as I said, Thomas describes
2 two sequences. He has the h5G1.1 which is the
3 humanized 5G1.1, and then he has the murine
4 5G1.1. So he describes both sequences. And
5 depending upon the actual delineation, one
6 could tell which one he's referring to.
7 Q. Let's take a look at the last
8 sentence of the abstract -- I'm sorry,
9 second-to-last sentence, the one that starts
10 "Finally":
11 "Finally, an intact humanized
12 h5G1.1 antibody blocked human complement
13 lytic activity at concentrations
14 identical to the original murine
15 monoclonal antibody."
16 Do you see that?
17 A. I do.
18 Q. And that's referring to
19 eculizumab?
20 A. No, it's not.
21 Q. Why not?
22 A. Well, there's no mention of
23 eculizumab in this document. And we know from
24 other publications, particularly Tacken, that
25 eculizumab is specifically a humanized 5G1.1

1 with a G2/G4 hybrid constant region.
2 So the G4 that's mentioned in
3 Thomas is not eculizumab, and a POSA would be
4 aware of that from subsequent citations in the
5 literature.
6 Q. So you agree that Thomas does not
7 refer to the name "eculizumab." Right?
8 A. Well, neither the name nor the
9 molecule itself that we know of as eculizumab,
10 based on the prior art of 2007.
11 Q. And do you understand that the
12 intact humanized h5G1.1 antibody referred to
13 by Thomas in this sentence is derived from the
14 original 5G1.1 mouse antibody? Right?
15 MR. KNAUSS: Object to the form.
16 You may answer.
17 A. Right. So as Thomas describes in
18 the abstract and in the publication, the
19 starting point was a murine sequence. CDR
20 grafting was carried out using the CDRs from
21 5G1.1 murine into human frameworks, and then
22 for the intact antibody, a human G4 was added.
23 So that is not eculizumab, but it is a
24 derivative of the 5G1.1 murine antibody.
25 Q. So the last sentence of the

1 abstract of Thomas:
2 "These results demonstrate that
3 humanized h5G1.1 and its recombinant
4 derivatives retain both the affinity and
5 blocking functions of the murine 5G1.1
6 antibody, and suggest that these
7 molecules may serve as potent inhibitors
8 of complement-mediated pathology in
9 human inflammatory diseases."
10 Do you see that?
11 A. I do.
12 Q. So a POSA would have understood
13 this sentence to mean that the full-length
14 intact humanized antibody described in Thomas
15 and derived from the mouse antibody was shown
16 to retain the same activity in blocking
17 C5-mediated cell lysis as the original mouse
18 antibody?
19 A. I think this sentence refers to
20 the CDRs of these 5G1.1, which are the murine
21 CDRs, in a humanized framework background,
22 retained the binding affinity and biological
23 activity of the murine antibody. So it's a
24 step that would be supportive of the fact that
25 these CDRs, in a framework grafted context,

1 have activity.
2 Q. Does Thomas mention CDRs in this
3 sentence?
4 A. Well, a POSA would understand
5 when you talk about humanization by CDR
6 grafting, that this is the result of that
7 response. And by reading the rest of the
8 paper, you don't stop at the abstract.
9 The rest of the paper indicates
10 that the framework changes that were
11 introduced had no impact. And Thomas also
12 makes it very clear that the Fabs behave the
13 same whether they're in the G4 background or
14 as isolated fragments.
15 So if you look at page 1394,
16 final paragraph, in contrast with what
17 Dr. Casadevall has said:
18 "Since choice of human antibody
19 isotype can influence antibody avidity,
20 whereas isotype choice does not
21 influence Fab affinity" -- citing to
22 Morelock 1994 -- "initial analysis of
23 the humanization procedure was performed
24 using humanized Fab fragments."
25 So that directly clarifies the

1 fact that Thomas did not consider that the
2 change in the constant domains for the heavy
3 chain would have an impact on Fab, and that was
4 known to one of skill in the art by 1994.
5 Q. Do Fab fragments have constant
6 region?
7 MR. KNAUSS: I didn't hear the
8 question. Do you mind repeating it?
9 Q. Do Fab fragments have a constant
10 region?
11 A. Yes. They have -- the light
12 chain has a constant region, and the heavy
13 chain has a CH1 domain. The CH2, CH3 domains,
14 which are the domains that are involved in Fc
15 receptor binding, for example, are absent from
16 a Fab fragment.
17 Q. And they're not full-length
18 antibodies. Right?
19 A. Fabs are not full length. But as
20 Thomas makes very clear here, the, well,
21 avidity may be -- change, and avidity is a
22 measure of multimerization, not of affinity.
23 Affinity is not changed by a selection of
24 isotype.
25 Q. All right. Let's go to page 1390

1 of Thomas. It's page 7 on the lower right.
2 A. Mm-hmm.
3 Q. And looking at the first full
4 paragraph in the left-hand column, it's about
5 the middle of the page. It says:
6 "The desired pharmacological
7 properties of complement inhibitors are
8 dramatically different for acute versus
9 chronic settings."
10 Do you see that?
11 A. I do.
12 Q. Do you agree?
13 A. It's consistent with what I said
14 earlier in my deposition that the PK
15 properties will depend upon the use that's
16 being contemplated for the molecule.
17 Q. It goes on to say:
18 "In acute settings, a complement
19 inhibitor should have a relatively short
20 serum half-life, coupled with a rapid
21 rate of tissue penetration since
22 complement activation occurs within the
23 tissue."
24 Right?
25 A. That's what it states in this

1 sentence, yes.
2 Q. Do you have any reason to
3 disagree with that statement?
4 A. No, I agree that if you -- in
5 acute settings, short half-life is often a
6 consideration.
7 Q. Two sentences down, right after
8 the cite to Yokota 1992.
9 A. Yes.
10 Q. The sentence reads:
11 "A complement inhibitor used in
12 chronic settings should have a prolonged
13 serum half-life and not provoke an
14 immune response."
15 Do you see that?
16 A. Yes.
17 Q. And do you agree with that
18 sentence?
19 A. As a monoclonal antibody, as we
20 discussed earlier, the goal is for PK
21 properties that you are designing as well as
22 not provoking a -- what's called a human
23 anti-mouse response.
24 Q. Do you agree that a full-length
25 antibody -- strike that.

1 Do you agree that a full-length
2 humanized antibody was the variant intended
3 for a chronic use setting according to Thomas?
4 A. Well, once again, it would depend
5 upon how the Fc domain was being developed.
6 And like I said, we certainly knew of ways of
7 modifying the Fc domain to either enhance or
8 reduce its half-life.
9 So there are other considerations
10 for Fab versus full-length antibodies that are
11 considered in addition to PK properties or PD
12 properties. Purification expression levels,
13 those are all other considerations that often
14 go into the calculation when one is developing
15 a potential therapeutic.
16 Q. There's a lot of parameters to
17 keep in mind in developing a therapeutic
18 antibody. Right?
19 A. No, not really. I think it's
20 quite a straight shot. We know what the
21 issues are in 2007, and we know which ones to
22 focus on to optimize a particular end result.
23 Q. Do you agree that full-length
24 humanized antibodies would typically have a
25 longer half-life than Fab or scFv fragments?

1 A. That's correct. Well, it depends
2 upon the species, but, yes, if they are
3 studied in intact animals, that would be the
4 case.
5 Q. All right. You already took me
6 here, but I'm going to take you back. Page
7 1394.
8 A. Yes.
9 Q. Page 11 on the bottom right.
10 A. Yes.
11 Q. (Reading): "Since choice of
12 human antibody isotype can influence antibody
13 avidity."
14 A. Correct.
15 Q. And you agree that choice of
16 isotype can influence antibody avidity?
17 A. By definition, an intact
18 antibody, as I think is being discussed in
19 this paragraph, would have two Fab binding
20 sites. And that differs from a single Fab
21 binding site that would be found and,
22 therefore, there is an avidity component that
23 results from the multimerization of binding
24 interactions.
25 So, in general, this is a

1 well-known phenomenon, and when antibody
2 engineers are developing therapeutic
3 antibodies, they do their affinity studies on
4 Fab fragments -- right? -- so as not to be
5 confounded by a avidity component.
6 This sentence goes on, I think,
7 importantly to stated that choice of the
8 isotype is not going to influence the Fab
9 affinity.
10 Q. So I may have missed it in there,
11 but are you agreeing that human -- choice of
12 human antibody isotype can influence antibody
13 avidity?
14 A. Yes. I think that's well-known.
15 For example, IgM forms pentameric or hexameric
16 structures. That has a very different avidity
17 than an IgG, which has a dimeric structure.
18 Right? An IgA will form dimers, so you have
19 four binding sites as opposed to two binding
20 sites. So isotype will influence avidity.
21 Q. Let's go to page 1396, page 13 on
22 the bottom right. Do you see the section
23 "Construction of a humanized h5G1.1 antibody"?
24 A. Yes, I do.
25 Q. And right below that section

1 header, Thomas says:
2 "Having demonstrated the effect
3 of humanization of the 5G1.1 variable
4 regions, an intact humanized antibody
5 (IgG4 isotype) was constructed and
6 produced in 293-EBNA cells."
7 Right?
8 A. I see that.
9 Q. So Thomas discusses an IgG4
10 isotype. Right?
11 A. That is correct.
12 Q. Does it discuss any other
13 isotype?
14 A. It -- the murine isotypes, of
15 course, but not for the humanized version.
16 That is the full-length G4 that it describes.
17 Q. Thanks for that clarification.
18 So Thomas doesn't discuss any
19 other human isotype?
20 A. Not that I've seen.
21 Q. How does Thomas refer to the IgG4
22 antibody?
23 A. h5G1.1 HuG4.
24 Q. And he calls it a humanized
25 antibody. Right?

1 A. Humanization is referring, I
2 think, in this context broadly to the CDR
3 grafting that he performed on the murine CDRs.
4 Q. The IgG4 antibody that Thomas is
5 discussing here is a full-length antibody.
6 Right?
7 A. (Document review.)
8 I don't see anywhere that Thomas
9 provides us with the full-length sequence of
10 the antibody. So the only information we have
11 is this sentence that says "an intact
12 humanized antibody IgG4 isotype was
13 constructed."
14 That's all the information we
15 have. I can't determine from that whether it's
16 intact, complete, or in any way modified.
17 Q. Okay. Other than that IgG4
18 isotype, does Thomas discuss any other
19 full-length antibodies?
20 A. In relation to the 5G1.1 you're
21 referring to?
22 Q. Yes.
23 A. Right. Because he discusses
24 murine intact antibodies as the initial
25 antibody that they started with and describes

1 studies that were done comparing the intact
2 murine antibodies to the humanized 5G1.1 Fabs
3 or intact antibody. But that's the only human
4 intact antibody I've seen in this publication.
5 Q. Okay. Did Thomas test the
6 humanized h5G1.1 HuG4 antibody against the
7 original murine 5G1.1 antibody?
8 A. Yes, he did. He describes
9 several experiments. So in the -- on page
10 1396, the paragraph we were looking at just
11 before, he says:
12 "The humanized h5G1.1 mAb had a
13 two-fold lower avidity than the murine
14 antibody. However, humanized 5G1.1 HuG4
15 antibody was equipotent with the murine
16 antibody at protecting PAEC from lysis
17 by human serum with a 0.5-fold molar
18 ratio of antibody to C5, completely
19 inhibiting lysis of the PAEC
20 (Figure 10)."
21 Q. That PAEC test was a test that
22 Thomas used to measure the ability of an
23 antibody to protect the million cells from
24 complement mediated damage. Right?
25 A. That's my understanding, yes.

1 Q. And so Thomas is saying that the
2 humanized IgG4 antibody was just as good at
3 protecting the million cells as the murine
4 antibody. Right?
5 A. As the murine parent antibody,
6 that's correct. Even though it had a
7 different avidity. So I think what he's
8 saying is that the avidity difference was not
9 biologically significant.
10 Q. Do you agree that Thomas is
11 discussing an antibody -- a humanized --
12 strike that.
13 Do you agree that Thomas is
14 discussing a humanized antibody that is
15 promising for therapeutic development?
16 MR. KNAUSS: Object to the form.
17 You may answer.
18 A. I think what Thomas says in the
19 abstract is that it suggests "these molecules
20 may serve as potent inhibitors of
21 complement-mediated pathology in human
22 inflammatory diseases."
23 So I think he's being circumspect
24 in terms of the overall utility of these
25 molecules, that they may have some role, but

1 he's not saying that they're promising
2 candidates for clinical development.
3 Q. Right. But he's not saying that
4 you should abandon this antibody. Right?
5 A. I think he's pointing to the
6 humanization of the Fabs as being on the route
7 to a potential therapeutic.
8 Q. Right. By Thomas' indication,
9 this was a good candidate to continue forward
10 with. Right?
11 A. I haven't seen any statements by
12 Thomas as to what his opinions were, but just
13 from the document itself, it demonstrates what
14 it shows, that the 5G1.1 CDRs in a human
15 framework context are able to retain their
16 binding affinity and ability to prevent the
17 activation of C5 cleavage in the in vitro
18 assays he describes.
19 Q. Curious, do all antibodies
20 directed to C5 prevent C5 cleavage?
21 A. No. I seem to recall discussions
22 in some of the publications I reviewed that
23 other antibodies have been described that do
24 not prevent C5 cleavage, that they don't bind
25 to the active site where cleavage occurs.

1 Q. Let's go to page 1397, page 14 on
2 the bottom right. And this is the sentence
3 that spans page 14 and page 15. And it reads:
4 "A clinically useful C5 inhibitor
5 must block generation of both C5a and
6 C5b-9, as both these molecules have
7 potent pro-inflammatory effects."
8 Right?
9 A. That's what it says, yes.
10 Q. Do you have any reason to
11 disagree with that sentence?
12 A. No. I think that's a reasonable
13 statement.
14 Q. Okay. Let's go down to page
15 1399, page 16 on the bottom right. About --
16 in the left-hand column about midway down,
17 there's a sentence that says:
18 "Firstly, the prolonged plasma
19 half-life."
20 Do you see that sentence?
21 A. Yes.
22 Q. The full sentence says:
23 "Firstly, the prolonged plasma
24 half-life of IgG is mediated through
25 binding of the Fc region to specific

1 'protection receptors' which have
2 recently been demonstrated to be
3 identical to the neonatal intestinal
4 transport receptor."
5 Do you see that?
6 A. I do.
7 Q. Is that sentence referring to --
8 strike that question.
9 Is that sentence saying that
10 binding of the Fc region is important to
11 prolonging plasma half-life -- half-life of an
12 IgG molecule?
13 A. That's what I was just referring
14 to before. That's talking about the FcRn
15 molecule. He's calling it a protection
16 receptor. So that is the FcRn molecule. And
17 it was known in -- by this point, 1996, that
18 the prolonged half-life of IgG, or the PK of
19 IgG was a result of FcRn binding that shuttles
20 the antibody away from the degradation pathway
21 inside cells to be recycled and released back
22 into the serum.
23 Q. So Fc region binding was
24 beneficial for prolonging half-life?
25 MR. KNAUSS: Object to the form.

1 You may answer.
2 A. The IgG Fc was known to be
3 involved in half-life determination by its
4 engagement with the neonatal Fc receptor,
5 which here is stated as the "protection
6 receptor" in quotes. That was known in 1996.
7 The observation that IgG had a
8 long serum half-life relative to other serum
9 proteins was described for us by Brambell some
10 20 years before.
11 So this was a known phenomenon,
12 that IgG antibodies had a property that was
13 unique among plasma proteins, shared only by
14 albumin.
15 Q. And that was mediated through
16 binding the Fc receptor?
17 A. FcRn.
18 Q. FcRn receptor?
19 A. Yes. It's a different receptor
20 than the Fc-gamma receptors that are involved
21 in inflammatory responses.
22 Q. All right. Moving on to the next
23 column on the right on page 1399. So the
24 first full paragraph about midway down, the
25 sentence starts "the human IgG4 isotype was

1 chosen."
2 Do you see that?
3 A. Yes.
4 Q. (Reading):
5 The human IgG4 isotype was
6 chosen, as this isotype does not
7 activate human complement" -- citing Tao
8 1993 -- "and there is only one known
9 allotype of IgG4" -- citing Ghanem in
10 1988 -- "precluding the potential
11 development of alloantibodies in
12 patients."
13 Right?
14 A. Yes.
15 Q. So that's referring to the IgG4
16 as having a reduced risk of immunogenicity in
17 humans. Right?
18 A. It's referring to its reduced
19 risk of activating complement through the
20 classical pathway as well as its reduced risk
21 of potentially inducing immunogenicity or
22 antibodies against the G4 constant domain.
23 Q. And Thomas describes that as why
24 the IgG4 isotype was chosen. Right?
25 A. That's the explanation he gives.

1 Q. And go down to the very end of
2 that paragraph. Thomas concludes:
3 "The h5G1.1 antibody is,
4 therefore, likely to be minimally
5 immunogenic in patients."
6 Right?
7 A. In this case, it's not clear if
8 he's referring to the Fab or the intact
9 antibody. Based on the previous sentence:
10 "Repeated administration of
11 chimeric antibodies containing intact
12 murine variable regions has induced an
13 immune response directed against the
14 murine variable region in nearly all
15 trials" -- referencing Khazaeli 1994.
16 "In this regard, it is significant that
17 introduction of murine amino acids in
18 the framework regions was not essential
19 for maintenance of high affinity binding
20 to C5. The h5G1.1 antibody is,
21 therefore, likely to be minimally
22 immunogenic in patients."
23 I believe he's referring to the
24 CDR grafted Fab in this case.
25 Q. And that's because of the

1 previous sentences?
2 A. Yes.
3 Q. Could he be referring to the
4 intact antibody?
5 A. It's ambiguous, I think, in this
6 context. When he refers to the intact
7 antibody, he does make it clear that it's the
8 human G4 in the nomenclature we've seen
9 before. The 5G1.1 in the absence HuG4 seems
10 to be his nomenclature for the Fab.
11 Q. Let's go back to your
12 declaration. So in the '880 declaration,
13 which is Tab 3, if we can go to paragraph 57,
14 which is on page 42, I believe, the last
15 sentence in that paragraph, you say:
16 "By 2007, three references --
17 Bell, Hillmen 2004, and Hill 2005" --
18 A. I'm sorry, I'm not with you.
19 MR. KNAUSS: We may have a page
20 versus paragraph --
21 A. Page 57 --
22 Q. Oh, I'm sorry. Page 42.
23 A. Oh, page 42. I'm sorry.
24 Q. Page 42.
25 A. I'm sorry. I was looking at page

1 57.
2 Q. We're looking at paragraph 57.
3 A. I got it. Thank you.
4 Q. All right.
5 A. Okay. Yes.
6 Q. And then we're going down to the
7 very last sentence of that paragraph, which
8 ends page 42:
9 "By 2007, three references --
10 Bell, Hillmen 2004, and Hill 2005 --
11 taught the use of pharmaceutical
12 compositions with antibody formulations
13 that are delivered intravenously to
14 treat PNH patients."
15 Right?
16 A. Yes.
17 Q. And you stand by that statement.
18 Right?
19 A. Yes.
20 Q. And you cite three references:
21 EX1007, EX1013, and EX1011. Right?
22 A. Yes.
23 Q. If we go back to pages 11 and 12
24 of your declaration -- I'm sorry -- pages 11
25 through 18, which is the table of exhibits.

1 A. Yes.
2 Q. EX1007 is Bell. Right?
3 A. Patent application, yes, to Bell.
4 Q. EX1013 is Hill 2005. Right?
5 A. Yes.
6 Q. And EX1011 is Hillmen 2004.
7 Right?
8 A. Yes.
9 Q. And you don't cite anything else
10 to support that sentence. Right?
11 A. (Document review.)
12 Yeah, I don't say this is the --
13 all the references, but these three certainly
14 were clear citations to the use of
15 formulations to treat PNH intravenously.
16 Q. Okay. Sitting here today, is
17 there anything, any reference that you would
18 like to add to the citation?
19 A. Not as I sit here today. These
20 three were certainly sufficient to provide the
21 basis for the obviousness arguments that I was
22 investigating.
23 (Ravetch Exhibit 18, Bell Patent
24 Application Publication Number US
25 2005/0191298, marked for identification,

1 as of this date.)
2 Q. So Exhibit 18 is the Bell patent
3 application publication we just referred to?
4 A. Yes.
5 Q. And has the publication
6 number US 2005/0191298. Right?
7 A. Yes.
8 Q. And you recognize this patent
9 application? Right?
10 A. I do.
11 Q. And you relied on this in your
12 declaration?
13 A. I cite to it in my declaration,
14 that's correct.
15 Q. Let's go down to paragraph 52 of
16 Bell. The last sentence spanning the
17 left-hand column to the right-hand column
18 reads:
19 "Particularly useful anti-C5
20 antibodies are h5G1.1-mAb, h5G1.1-scFv,
21 and other functional fragments of
22 h5G1.1. Methods for the preparation of
23 h5G1.1-mAb, h5G1.1-scFv, and other
24 functional fragments of h5G1.1 are
25 described in" -- and then it cites the

1 Evans patent. Right?
2 A. Yes.
3 Q. And the Thomas article we just
4 looked at. Right?
5 A. Yes.
6 Q. And the very last sentence of
7 paragraph 52, it reads:
8 "The antibody h5G1.1-mAb is
9 currently undergoing clinical trials
10 under the trade name eculizumab."
11 Right?
12 A. Yes.
13 Q. Is Bell referring to the
14 antibodies described in Thomas there?
15 A. The CDR grafting -- the CDRs in
16 Thomas I believe are what he's referring to.
17 It's the humanized sequences of Evans that are
18 in the '245 patent that are incorporated into
19 the eculizumab.
20 So as I said before, Thomas does
21 not use the term "eculizumab," nor does he use
22 the term "h5G1.1-mAb" in his publication. So
23 that nomenclature is now being defined in Bell
24 as being eculizumab, and it points us to the
25 Evans reference and the CDRs that were used in

1 Thomas in the Evans publication.
2 Q. The terminology h5G1.1-mAb, would
3 you consider that an intact full-length
4 antibody?
5 A. It's not -- it's only defined
6 here as being trademarked under the name
7 eculizumab. And if we now look to see what is
8 known about eculizumab in this time frame, by
9 2007, we're instructed by Tacken quite clearly
10 that that's referring to a human G -- a human
11 5G1.1 with the G2/G4 hybrid sequence.
12 So it would be clear to a POSA in
13 looking at this sentence that what's relevant
14 is the term "eculizumab" and that it's a
15 humanized 5G1.1 of the Evans family, and then
16 it has the Tacken characterization of having a
17 hybrid G2/G4 Fc.
18 Q. And then -- so in your opinion,
19 why wouldn't the h5G1.1-mAb be referring to
20 something that Thomas discussed?
21 A. Well, I don't believe Thomas
22 discusses this term at all. He calls it -- if
23 he calls an intact antibody, he calls it human
24 G4. We've seen that in the publication.
25 So there's nothing in Thomas that

1 would lead me to believe that this antibody is
2 similar or identical to any of the Thomas
3 antibodies and that the relevant combination
4 that I reviewed was clearly explicitly
5 defining eculizumab. And Thomas does not
6 define eculizumab.
7 Q. And are you saying that just
8 referring to h5G1.1-mAb, you're not certain
9 what that antibody is?
10 A. No. It's eculizumab.
11 Q. What's the sequence of that
12 antibody?
13 A. Well, that's what the analysis
14 that I carried out in my declaration informs
15 us. By using the '245 sequences of the scFvs
16 together with -- in one application, together
17 with the knowledge that eculizumab has a G2/G4
18 hybrid sequence, I was able to derive a
19 sequence that, when I compared it to the '149
20 SEQ ID 2 and 4, matched the molecule that is
21 defined in that claim.
22 Q. And what gives you the knowledge
23 that eculizumab has a G2/G4?
24 A. Tacken.
25 Q. And when did you learn of Tacken?

1 A. I learned of Tacken a long time
2 ago. Tacken actually references our work.
3 Tacken is related to dendritic cell activation
4 through the molecule called DC-SIGN, and we
5 had published that pathway years before
6 Tacken.
7 So I was aware of Tacken's
8 interest in the pathway, and I was, therefore,
9 aware of the Tacken reference quite a while
10 ago.
11 Q. All right. So looking at Bell as
12 a whole, where does Bell provide an amino acid
13 sequence?
14 MR. KNAUSS: Asked and answered.
15 You may answer, Dr. Ravetch.
16 A. Yeah, so Bell explains to us
17 clearly on paragraph -- or Column 5 that the
18 molecule that he's studying is eculizumab,
19 which has a clinical properties for the
20 treatment of PNH in this trial, and that it
21 directs us to the sequences in the Evans
22 patent.
23 And the term "eculizumab," as I
24 said, by 2005, was known to have a hybrid
25 G2/G4 sequence, which actually Tacken

1 references Mueller to give us a full sequence.
2 So it's a simple matter for a
3 POSA to construct a sequence based on the '245
4 patent and the Mueller patent to arrive at a
5 sequence that, when then compared to claims in
6 the '880 patent that references Sequence 2 and
7 4, would, in fact, match.
8 Q. Bell only cites to Thomas and
9 Evans here. Right?
10 A. And he gives the term
11 "eculizumab." Right.
12 Q. Okay.
13 A. So one of skill in the art would
14 see that name and immediately be motivated to
15 find the term "eculizumab" in the literature,
16 which one would find in Tacken.
17 Q. Okay. But my answer -- my
18 question is a little bit more simpler than
19 that. Only Evans and Thomas is cited here in
20 Bell. Right?
21 A. The citations to Evans and Thomas
22 are part of the disclosure in Bell as to what
23 h5G1.1-mAb is. That is not the complete
24 definition. It includes the term
25 "eculizumab." And that's a critical component

1 in order to understand what Bell is talking
2 about.
3 Q. And in your opinion, the
4 sequences incorporated into Bell are the
5 sequences of Thomas and Evans. Right?
6 A. He incorporates those sequences,
7 and he also defines a product with the
8 trademark name "eculizumab." So one cannot
9 read that out of the description. It's part
10 of the description.
11 And since Thomas does not use the
12 term "eculizumab," one would not look at
13 Thomas for the structure of eculizumab.
14 THE VIDEOGRAPHER: You have five
15 minutes left.
16 THE WITNESS: Five minutes left.
17 MR. KNAUSS: Should we take a
18 break?
19 MR. COCHRAN: Yeah, take a break.
20 THE WITNESS: That's a good
21 thing. Thank you.
22 THE VIDEOGRAPHER: The time now
23 is 10:59 a.m. This concludes Media 2.
24 Off the record.
25 (Recess taken from 10:59 a.m. to

1 11:20 a.m.)
2 THE VIDEOGRAPHER: The time now
3 is 11:20 a.m. This begins Media 3. On
4 the record.
5 BY MR. COCHRAN:
6 Q. All right. Dr. Ravetch, let's go
7 back to Thomas. And then, can you please turn
8 to page 1393, page 13 on the bottom right.
9 In the section right above
10 "Discussion," do you see that Thomas refers to
11 "the humanized h5G1.1-mAb." Right?
12 A. I see that.
13 Q. What is that antibody?
14 A. Well, if you look in other places
15 in the document, he uses that terminology to
16 describe the Fab. So, for example, Figure 3,
17 he says "Inhibition of 5G1.1 mAb binding," and
18 he describes Fab binding curves.
19 If you -- so I think that that
20 term, as I said earlier, in Thomas seems to
21 refer to Fab in some of the figures, but the
22 human 5G1.1 HuG4 he uses to refer to the
23 intact antibody.
24 Q. Does he ever use h5G1.1 Fab?
25 A. Yes, he uses that, for example,

1 in the Figure 3. He describes the experiment
2 as 5G1.1-mAb binding, and then in the actual
3 figure itself, defining the various curves, he
4 calls them Fab, Fab CDR, CDR plus FW. So he's
5 using mAb to include all of those different
6 Fabs.
7 Q. So when Thomas wants to refer to
8 the Fabs, he says Fab?
9 A. No. He says mAb as well.
10 Q. Go down to the description of
11 Figure 9. This is on page 1398, or page 15 on
12 the bottom right.
13 A. Yes.
14 Q. Figure 9 refers to h5G1.1 HuG4
15 mAb. Right?
16 A. Well, it's actually -- it says
17 "Inhibition of 5G1.1 mAb." So it doesn't even
18 use the h5G1.1.
19 Q. I'm looking a little further
20 down.
21 A. And then, in the second sentence,
22 he says 5 -- "h5G1.1 HuG4." All right. Then
23 he goes on to use terminology.
24 So there's an inconsistency in
25 the use of his terminology within the same

1 figure, let alone between figures. So I
2 think one could say it depends on the specific
3 context of his experiment.
4 But there certainly is no
5 consistent nomenclature that identifies
6 5G1.1-mAb as being an intact antibody. It's
7 also used as scFv in Figure 5, for example.
8 So there's Fab, there's scFv, there's intact
9 G4. It's all used interchangeably with the
10 5G1.1-mAb.
11 MR COCHRAN: All right. Let's
12 put Thomas to the side again.
13 MR. KNAUSS: Thank you.
14 (Ravetch Exhibit 19, Reference by
15 Anita Hill et al. titled "Sustained
16 response and long-term safety of
17 eculizumab and paroxysmal nocturnal
18 hemoglobinuria" from 2005, marked for
19 identification, as of this date.)
20 Q. So I've marked as Exhibit 19 a
21 reference by Anita Hill et al. from 2005
22 titled "Sustained response and long-term
23 safety of eculizumab and paroxysmal nocturnal
24 hemoglobinuria."
25 And this bears Exhibit

1 Number 1013. Do you recognize this document?
2 A. Yes, I do.
3 Q. Do you rely on this document in
4 your declarations for these proceedings?
5 A. Yes. I cite to this document in
6 the declaration for the '809 patent.
7 Q. Lets take a look at the
8 introduction in the column on the right,
9 paragraph that starts with "eculizumab." It
10 states:
11 "Eculizumab is a humanized
12 monoclonal antibody that specifically
13 targets the complement protein C5 and
14 prevents its cleavage."
15 Right?
16 A. Yes, that's what it says.
17 Q. And that's referring to the Fab
18 fragment?
19 A. No.
20 MR. KNAUSS: Object to the form.
21 You may answer.
22 A. I'm sorry.
23 It says it's eculizumab. It's
24 not referring to a Fab fragment. It's
25 referring to eculizumab. And as I said, using

1 eculizumab terminology, we know that refers to
2 the humanized intact antibody with a G2/G4
3 constant region.
4 Q. And you get that from Tacken.
5 Right?
6 A. Yes.
7 Q. We'll get to Tacken eventually.
8 You see that that sentence on
9 what eculizumab is is followed by a citation.
10 Right?
11 A. Yes, I do.
12 Q. And that's Citation 9. Right?
13 A. Yes.
14 Q. And what is Citation 9?
15 A. Thomas.
16 Q. So Hill is citing to Thomas, is
17 describing that:
18 "Eculizumab is a humanized
19 monoclonal antibody that specifically
20 targets the complement protein C5 and
21 prevents its cleavage."
22 Right?
23 A. That's what Thomas -- that's what
24 Hill is citing to in this sentence. But as
25 I've stated earlier, Thomas does not refer to

1 eculizumab anywhere in the document.
2 Q. Does Hill 2005 disclose an amino
3 acid sequence?
4 A. (Document review.)
5 So my purpose in citing to Hill
6 in my declaration is provided on page 105 of
7 my declaration for the '809 patent where,
8 under Ground 3, I am citing to Hill for the
9 statement:
10 "Claim 16 recites the additional
11 limitation that the patient has less
12 than a 3 percent likelihood of
13 developing antibodies to the antibody
14 that binds C5 after 26 weeks of
15 treatment."
16 And that's a limitation that
17 "Hill reports in the Phase II trial, that after
18 12 months of eculizumab treatment, no patients
19 were antibodies against eculizumab detected."
20 So that was my -- that's why I'm
21 relying upon Hill to provide in terms of my
22 obviousness analysis.
23 Q. Sure. That wasn't may question
24 though. Does Hill disclose an amino acid
25 sequence?

1 A. So Hill, once again, is part of
2 the collection of documents that I've used in
3 my obviousness analysis to determine the
4 sequence of eculizumab. Hill does not
5 expressly define eculizumab. That is defined,
6 as I've stated in my declarations, by Tacken
7 and Bell and Evans.
8 Q. But Hill does refer to Thomas
9 when it mentions eculizumab though. Right?
10 A. Hill refers to Thomas when it
11 mentions eculizumab, and my understanding of
12 that is, once again, Hill is not a publication
13 that attempts to define the structure of
14 eculizumab. It's reporting a clinical trial.
15 And it's -- the citation would be
16 to the predecessor molecules that target C5 in
17 preventing its cleavage. That's how I would
18 read that sentence, not as a disclosure for
19 the sequence itself.
20 (Ravetch Exhibit 20, "Effect of
21 Eculizumab on Hemolysis and Transfusion
22 Requirements in Patients with Paroxysmal
23 Nocturnal Hemoglobinuria" by Peter
24 Hillmen et al., marked for
25 identification, as of this date.)

1 Q. So we've marked as Exhibit 20 an
2 article by Peter Hillmen et al. from 2004,
3 titled effect -- excuse me -- "Effect of
4 Eculizumab on Hemolysis and Transfusion
5 Requirements in Patients with PNH."
6 Do you recognize this document?
7 A. Yes, I do.
8 Q. Did you rely on this document in
9 your declarations?
10 A. I relied upon it in the
11 declaration for the '809 Patent claims.
12 Q. You can go to page 553 of
13 Hillmen, which is page 4 on the lower right.
14 And do you see the paragraph that starts with
15 "Eculizumab"?
16 A. Yes, I do.
17 Q. That first sentence reads:
18 "Eculizumab is a recombinant
19 humanized monoclonal antibody that was
20 designed to block the activation of
21 terminal complement components."
22 Right?
23 A. Yes.
24 Q. What is eculizumab referred to
25 there? What is the eculizumab referred to

1 there?
2 A. What is it referred to?
3 Q. What --
4 A. I don't understand the question.
5 Eculizumab is cited here and --
6 Q. What is Hillmen referring to when
7 Hillmen says "eculizumab"?
8 A. He's saying it's a recombinant
9 humanized monoclonal antibody. And it has
10 activity to block terminal complement
11 components. Right?
12 Q. Does Hillmen disclose the
13 sequence of eculizumab?
14 A. Once again, this is a publication
15 describing the same clinical trial that we've
16 seen in Hill as well as in Bell to describe
17 the clinical activity of the eculizumab
18 antibody. And it's not a publication to
19 describe the structure of eculizumab.
20 Q. Typically, you're not
21 investigating the structure of an antibody
22 when you're in clinical trials. Right?
23 MR. KNAUSS: Object to the form.
24 A. The audience for this publication
25 are clinicians who are interested in the

1 treatment of PNH. Their focus is on the
2 clinical results of the product.
3 And the product is defined simply
4 as being a monoclonal antibody that's
5 humanized that blocks the activation of
6 complement components.
7 And I think there's no intent to
8 provide a full structure for eculizumab, and
9 we know that from the Citation Number 14,
10 which is to Riechmann. Riechmann has nothing
11 to do with eculizumab or to 5G1.1. Riechmann
12 is simply CDR grafting with framework
13 modifications, and 15 is Thomas once again.
14 So from this we would say this is
15 giving you the background to an antibody CDR
16 that has a capacity to engage human C5 and
17 block its cleavage by convertase.
18 Q. So you agree that when Hillmen
19 mentions eculizumab here, Hillmen points you
20 to Thomas. Right?
21 A. The citation is to Riechmann and
22 Thomas. The citation is not to the structure
23 of eculizumab. It's to the background of what
24 eculizumab was derived from, which, of course,
25 is the CDRs of Thomas through the humanization

1 process of Riechmann.
2 Q. You don't disagree that it does
3 point you to Thomas though. Right?
4 A. I disagree that this is a
5 definitive citation. This is not what a POSA
6 would use to understand what eculizumab is. A
7 POSA interested in defining the structure of
8 eculizumab would not rely upon Hillmen for
9 that information, as I have not relied upon it
10 for my analysis of the sequence of eculizumab.
11 Q. Do you think this is an
12 inaccurate citation by Hillmen?
13 A. It serves the purpose of Hillmen
14 in the context of what he is reporting which
15 is a clinical trial. He's giving his audience
16 the background to explain that this antibody
17 has activity against complement components.
18 And from the point of view of the
19 audience he is addressing, that is fine. From
20 the point of view of a POSA who wants to
21 obtain the sequence of eculizumab, it's not a
22 disclosure which is of particular relevance.
23 Q. And why would a POSA want to
24 obtain the sequence of eculizumab?
25 A. Because of the clinical trial

1 results, because a POSA would be motivated to
2 obtain an antibody that has the activity
3 described in Hill, in Hillmen, in Bell, to
4 block the paroxysms seen in PNH.
5 Q. And Bell, Hillmen, and Hill all
6 cite to Thomas. Right?
7 A. For the prior background of how
8 the program was initiated, that it starts
9 with -- that it's a monoclonal antibody. It's
10 not a small molecule inhibitor. It's not a
11 polyclonal preparation. It's a monoclonal,
12 it's a recombinant.
13 All of that is appropriate for
14 the audience that's being addressed. But as a
15 POSA who would be interested in saying, Yes,
16 this is an antibody that would be of interest
17 to obtain, this citation would not be relied
18 upon.
19 Q. So does Hillmen say that he's
20 only relying on Thomas for background
21 information?
22 A. He doesn't have to. He makes it
23 clear from this one sentence that's all he's
24 providing. This is the minimal definition.
25 It's a "recombinant humanized monoclonal

1 antibody designed to block the activation of
2 terminal complement components."
3 And from that point of view,
4 Riechmann is a citation to antibody
5 humanization. You know, Thomas is a citation
6 to a particular monoclonal antibody with CDRs
7 that have the binding specificity. Right?
8 That's sufficient, I believe, for Hillmen to
9 provide to his readership.
10 Q. Let's go back to Thomas real
11 quick.
12 MR. KNAUSS: (Handing.)
13 THE WITNESS: Thank you.
14 Q. So as a POSA reading Thomas, when
15 developing a therapeutic antibody against C5,
16 where would you go from here after Thomas?
17 A. Well, you wouldn't go to Thomas.
18 Q. Well, I'm asking if you were --
19 A. As a POSA, you're asking me as a
20 POSA, in 2007, interested in eculizumab based
21 on Bell, for example, or Hillmen or Hill, all
22 of whom are reporting clinical trial results,
23 a POSA would go from Bell to the Evans
24 disclosure.
25 Evans is the most pertinent

1 reference from a POSA's perspective. And from
2 there, Tacken would be an obvious connection
3 to define Mueller, which is the G2/G4 hybrid
4 Fc.
5 So a POSA would not start at
6 Thomas for a simple reason that there's
7 nothing in Thomas that would say anything
8 about eculizumab.
9 Q. Sure. But Hill, Hillmen, and
10 Bell all point you to Thomas -- right? --
11 we've established that?
12 A. They cite to Thomas, but Bell
13 more specifically cites to Evans.
14 Q. So as a POSA investigating
15 eculizumab, reading Hillmen, for example,
16 seeing the citation to Thomas, you would go to
17 Thomas first. Right?
18 A. No, I disagree. In fact, you
19 would be discouraged from doing that because
20 when Evans was issued as a Patent in 2002, the
21 Patent owner, Alexion, said Evans discloses
22 eculizumab.
23 So a POSA would know Alexion did
24 not say Thomas discloses eculizumab, Evans
25 discloses eculizumab. So a POSA with

1 knowledge of the literature, interested in
2 eculizumab, would be directed from the Patent
3 owner to eculizumab as the Evans Patent has
4 described it.
5 Q. So you were relying on that
6 statement by Alexion that Evans discloses
7 eculizumab?
8 A. No, it's supportive of that, and
9 we know from Bell that Bell says explicitly
10 that the 5G1.1 antibody disclosed in Evans is
11 currently trademark of eculizumab undergoing
12 clinical trials.
13 So it's part of the documentation
14 that informs a POSA how to understand
15 eculizumab.
16 Q. Are you saying that -- so it's
17 your opinion, Dr. Ravetch, that a person of
18 ordinary skill in the art reading, for
19 example, Hillmen, and reading the sentence
20 about eculizumab that cites to Thomas, a POSA
21 would not go to Thomas and read what Thomas
22 had to say. Right?
23 A. A POSA might read it but say,
24 This is not eculizumab. Let me see if there's
25 a reference that identifies eculizumab. And

1 you would find that in Bell, not in Thomas.
2 Q. How would a POSA not know -- how
3 would a POSA know that Thomas does not
4 describe eculizumab?
5 A. It doesn't say it's eculizumab,
6 very simply. And while a POSA would look at
7 Bell, which he'd also look at -- I mean, you
8 can't exclude Bell. He'd look at Bell, he'd
9 look at Hill and Hillmen, and he'd look at
10 Bell and Bell, and say Bell explicitly relates
11 eculizumab to the 5G1.1 humanized antibody as
12 disclosed in Evans.
13 So Bell would be the starting
14 point, you know, with Hill and Hillmen, you
15 know, supporting the interest in an antibody
16 that has a clinical activity described in
17 those studies.
18 But it was Bell that gave the
19 POSA that motivation to say the Evans
20 disclosure is most relevant, and the fact that
21 Alexion also pointed to Evans, you know,
22 doesn't hurt.
23 Q. Bell also cites Thomas, though.
24 Right?
25 A. Right, but when it comes to

1 eculizumab, it's clear that the Evans
2 publication is the one that is relevant, as
3 Alexion has instructed us. Among others.
4 Q. When did Alexion instruct us
5 about that?
6 A. When -- well, let's go look at my
7 expert report.
8 (Document review.)
9 Q. When you get there, please tell
10 me where you are.
11 A. I will.
12 (Document review.)
13 Page 45, paragraph 64.
14 Q. Of which?
15 A. Of my '149 declaration.
16 Q. Which paragraph, I'm sorry?
17 A. I'm sorry, it's on page 45,
18 paragraph 64 of the '149. So what I state
19 here is that:
20 "In 2002, Alexion also announced
21 the issuance of the Evans patent, which
22 Alexion said 'covers the composition and
23 use of Alexion's lead drug candidate
24 eculizumab (formally known as 5G1.1).'"
25 And I point to Exhibit 1020, also

1 Exhibit 1022. And -- right. Those are the
2 references.
3 Q. All right.
4 A. So -- and then, of course, in
5 paragraph 65 we talk about the Kaplan
6 reference which equates human 5G1.1 and
7 eculizumab as "synonyms."
8 So the persuasive evidence in the
9 prior art, going back to 2002 and certainly by
10 2007, was that it's Evans that discloses the
11 compositions of Alexion's lead candidate
12 eculizumab, and from there, we, as we said,
13 can find citations like Tacken that describe
14 the Fc portion of that antibody being a
15 hybrid, referencing Mueller, for that
16 structure.
17 Q. So paragraph 64 of your
18 declaration you just pointed me to, what is
19 your understanding of the words that Alexion
20 used that the Evans patent "covers the
21 composition and use of Alexion's lead drug
22 candidate"?
23 A. I didn't offer an opinion as to
24 that particular language. I think it states
25 what it states, that the patent relates

1 directly to eculizumab.
2 Q. So you don't have a --
3 A. And Evan -- and Alexion does not
4 cite to Thomas for that because Thomas does
5 not disclose eculizumab, Evans does.
6 Q. Sitting here today, you don't
7 have an opinion on what the term --
8 terminology "covers the composition and use"
9 means?
10 A. I think when a claim covers a
11 particular product, I believe that's a legal
12 terminology. And I'm a scientist, I'm not a
13 lawyer, Counselor, so I'm not going to offer
14 an opinion as to what the scope of the
15 coverage of a claim term might be.
16 Except as a scientist, reading
17 this, I would understand that if one is
18 interested in determining the sequence of
19 eculizumab, among other citations, Alexion
20 confirms that the Evans is a relevant source.
21 (Ravetch Exhibit 21, US Patent
22 Number 6,355,245 B1, marked for
23 identification, as of this date.)
24 Q. What's marked as Exhibit 21, the
25 Evans patent, Patent Number 6,355,245.

1 Do you recognize this patent?
2 A. Yes, I do.
3 Q. Is this the Evans patent you were
4 just referring to?
5 A. Yes, it is.
6 Q. And you relied on this Patent in
7 your declarations. Right?
8 A. Yes, I did.
9 Q. And according to you, this is
10 relevant for determining what eculizumab is.
11 Right?
12 A. The sequence of eculizumab,
13 that's correct.
14 Q. Evans does not disclose any
15 full-length humanized antibody. Right?
16 A. Evans discloses the so-called
17 scFv's as well as other fragments and
18 explicitly states that these can be combined
19 with constant regions to develop full-length
20 antibodies.
21 Q. Right. So the question was a
22 little bit more specific than that.
23 Evans does not actually disclose
24 a full-length humanized amino acid sequence.
25 Right?

1 MR. KNAUSS: Object to the form.
2 You may answer.
3 A. (Document review.)
4 My review of the disclosed
5 sequence is they're all fragments, scFvs or
6 Fds.
7 Q. So Evans does not disclose a
8 full-length humanized amino acid sequence of
9 an antibody. Right?
10 MR. KNAUSS: Object to the form.
11 You may answer.
12 A. Evans does not disclose a
13 full-length antibody sequence in the context
14 of the anti-C5 antibodies he's studying.
15 Q. Well, Thomas -- Evans does
16 disclose a full-length mouse antibody. Right?
17 A. Can you point me to that,
18 Counselor?
19 Q. Figures 18 and 19.
20 A. Excuse me?
21 Q. Figures 18 and 19. And if it
22 also helps, you can refer to the descriptions
23 of Figures 18 and 19 at Columns 9 and 10.
24 A. These aren't full-length
25 antibodies, Counselor. These are only

1 variable regions.
2 Q. Thank you --
3 A. You asked for a full-length
4 antibody.
5 Q. Thank you for --
6 A. These are not full-length
7 antibodies.
8 Q. Figure 18 discloses the light
9 chain variable region of the antibody 5G1.1.
10 Right?
11 A. The light chain variable region
12 doesn't include the constant region of the
13 light chain. Right? And --
14 Q. Figure 19 is the heavy chain
15 variable region?
16 A. Which does not contain the
17 constant regions.
18 Q. Right.
19 A. So neither 18 nor 19 disclose a
20 full-length antibody. Therefore, nothing in
21 Evans discloses a full-length antibody,
22 neither murine, nor humanized, nor anything
23 else.
24 Q. Okay. Can you point me to where
25 Evans says "eculizumab"?

1 A. Evans does not recite eculizumab,
2 as I recall. It recites the 5G1.1 humanized
3 antibodies and describes exemplary sequences
4 of humanized scFvs and humanized light chain
5 sequences.
6 Q. So as a POSA, in the 2007 time
7 frame, reading a clinical trial result like
8 Hillmen, for example, that we looked at.
9 Right?
10 A. Or Bell.
11 Q. Or Bell.
12 A. Right.
13 Q. Or Hill.
14 A. Or Hill.
15 Q. It is your opinion that those
16 clinical trials would encourage you to go look
17 for the sequence of eculizumab. Right?
18 A. That's correct.
19 Q. And each of Bell, Hillmen, and
20 Hill cite to Thomas. Right?
21 MR. KNAUSS: Asked and answered.
22 A. Yes, so as I said, in looking for
23 the sequence of eculizumab, I would not rely
24 on Hillmen or Hill. I rely on Bell who
25 explicitly describes the human 5G1.1 antibody

1 known as eculizumab and cites to the Evans
2 reference that we're looking at right now.
3 Q. So --
4 A. Hill and Hillmen do not equate
5 5G1.1 with eculizumab. They don't provide the
6 path that a POSA would take to try to
7 determine what is the sequence of eculizumab.
8 Q. Okay. So as a POSA, you would
9 read Bell --
10 A. Yes.
11 Q. -- be led to Evans --
12 A. Yes.
13 Q. -- which does not disclose any
14 full-length antibodies. Right?
15 A. That's correct. But you wouldn't
16 stop there. You would continue your search of
17 eculizumab and find Tacken, who explicitly
18 tells you that it's a G2/G4 Fc and refers you
19 to Mueller.
20 Q. Does Evans direct you to Tacken?
21 A. Evans does not direct you to
22 Tacken.
23 Q. Let's go to Column 42 of Evans.
24 Do you see Example 11 down there at the
25 bottom?

1 A. Yes.
2 Q. All right. Let's follow that
3 onto the next page. And Example 11 is
4 disclosing 18 scFv fragments. Right?
5 A. That's correct. No, that's not
6 correct. Some are scFv, some are Fds. It
7 depends on the specific construct. They
8 all -- they are all referring to recombinant
9 antibodies that have the 5G1.1 CDRs.
10 Q. So aside from the CDRs, all 18
11 are a bit different though. Right?
12 MR. KNAUSS: Object to the form.
13 A. There are differences among the
14 various sequences. They're all quite related,
15 of course, because they're based on the CDRs
16 and they're based on humanized framework
17 sequences, but there are differences between
18 some of these elements, yes.
19 Q. And which of the 18 did Evans
20 test?
21 A. (Document review.)
22 Q. And feel free to read what you
23 want, but you might find an answer in Example
24 12.
25 A. (Document review.)

1 So the testing that was done in
2 Example 12 is the murine scFv. Right? Now,
3 there are other antibodies that are tested in
4 Example 15. The N18-8 is another antibody to
5 C5 that's tested. Various Fds are tested in
6 that example as well. So that seems to be
7 what's disclosed in Evans.
8 Q. Okay. The murine 5G1.1 scFv that
9 was tested in Example 11 -- I'm sorry --
10 tested in Example 12 is the first scFv
11 mentioned in Example 11. Right?
12 A. I don't know if it's the same
13 one, but it certainly is mentioned in Example
14 11 as a "murine scFv designated 5G11.1M1scFv
15 (SEQ ID 7)." In Example 12 it doesn't use
16 that nomenclature. It just says "m5G1.1
17 scFv."
18 Q. You can't tell by nomenclature
19 alone what the antibody is?
20 MR. KNAUSS: Object to the form.
21 A. There are other murine constructs
22 in Example 11 that have different
23 nomenclature. So one would have to assume
24 that that is related. I think what's critical
25 about this experiment is the analysis of the

1 CDR specificity and their activity as
2 single-chain Fvs. And that's what's being
3 pointed to in this experiment.
4 Q. Right. But going back to my more
5 specific question, you're saying that when you
6 see a nomenclature for a particular antibody,
7 you can't be certain which antibody that is?
8 A. No, that's not true. It's quite
9 explicit in Example 11 what the antibodies
10 are. They're given their sequence IDs. You
11 know precisely what you're talking about in
12 those experiments.
13 And in other citations, we know
14 exactly what the eculizumab is referring to as
15 a human 5G1.1, with the sequences that are
16 found in Evans and the Fc that's described by
17 Tacken.
18 So it's not a general statement
19 that an antibody sequence -- an antibody name
20 does not reveal its sequence. It can.
21 Q. Does Evans disclose testing of
22 any of the other 17 fragments discussed in
23 Example 11?
24 A. On my review of the
25 specification, I don't see -- I do see some

1 examples for Example 15 and Example 14.
2 In Example 14, it's unclear
3 precisely what's being tested:
4 "The results of these assays show
5 that the 5G1.1 mAb inhibited binding of
6 purified human C5 to either C3 or C4 by
7 at least 60 to 90 percent."
8 Q. Right. You're saying that the
9 reference to 5G1.1 mAb, you're not sure what
10 that is. Right?
11 A. Well, it just says -- I think
12 it's "5G1.1 Fab (derived from 5G1.1 by
13 conventional papain digestion)."
14 So I think a POSA would
15 understand that to mean that you start with
16 the murine antibody, carry out a standard
17 papain digestion to get the Fab fragment, that
18 it's not a recombinant fragment, as opposed to
19 the examples in 11 which are all recombinant
20 fragments.
21 Q. Except 14 doesn't say so. Well,
22 never mind. Strike that question.
23 So as a POSA looking at Example
24 11 and the fragments described therein, Evans
25 doesn't point you to which one to continue

1 testing. Right?
2 MR. KNAUSS: Object to the form.
3 You may answer.
4 A. What do you mean by "testing"?
5 Q. Does Evans point a POSA to any
6 particular one of the 18 to say that one is
7 better than another?
8 A. In the context of what kind of an
9 assay? I'm not understanding the question,
10 Counselor.
11 Q. I'm just trying to compare the 18
12 fragments and trying to get an understanding
13 as a -- from a perspective of a POSA, if there
14 is one particular fragment disclosed in Evans
15 Example 11 that would immediately be
16 recognizable as a promising candidate for,
17 let's say, a therapeutic use.
18 A. Right. So like I said, Evans is
19 guidance to the structure of eculizumab.
20 That's what Mueller has -- sorry -- that's
21 what Bell has informed us -- right? -- is the
22 structure of eculizumab. And of those 18
23 constructs, nine them are humanized scFvs or
24 similar molecules.
25 So you immediately are pointed to

1 the nonhumanized because you know from Bell
2 that eculizumab is a human 5G1.1 -- humanized
3 5G1.1 now known as eculizumab.
4 So you'd reduce your 18 to nine.
5 Right? Those nine, as I've stated in my
6 report, would be potential candidates for
7 generating a sequence that one can then later
8 compare to the asserted claims and determine
9 if those sequences are matching or not.
10 We can go further because we know
11 from Mueller, that there's a -- there is a
12 preferred sequence in that list. And that's
13 the SEQ ID 20. And with a knowledge of
14 Mueller, we would take Evans and look at that
15 one as our preferred.
16 But if you had to make all nine,
17 it's not a unreasonable amount of effort, and
18 you have a reasonable expectation of success
19 in obtaining a sequence that would have the
20 humanized 5G1.1 with the Fc domain that Tacken
21 has directed you to.
22 Q. But sticking just with Evans and
23 of the nine that you just mentioned, nothing
24 in Evans points you in the direction of one
25 particular fragment. Right?

1 MR. KNAUSS: Asked and answered.
2 A. Once again, my citation to Evans
3 is not to say that it stands on its own.
4 Evans, to a POSA, would be something that
5 would be relevant prior art in determining the
6 sequence of eculizumab and would then develop
7 a sequence that would render the claims
8 obvious.
9 MR. COCHRAN: I just have a few
10 more questions on this section and then
11 we can probably break for lunch. Is
12 that all right?
13 THE WITNESS: I can use a
14 bathroom break also.
15 MR. COCHRAN: I will take that
16 into consideration.
17 THE WITNESS: Thank you.
18 Q. Let's go to Column 49 of Evans
19 and Example 12.
20 A. Yes.
21 Q. And Example 12 is testing the
22 m5G1.1 scFv. Right?
23 A. Yes.
24 Q. And it compares that to the --
25 one second -- test results for the antibody

1 named N19/8. Right?
2 A. It says:
3 "Direct comparison to the
4 efficacy of m5G1.1 scFv to the 5G1.1 mAb
5 and Fab demonstrated that the m5G1.1
6 scFv completely blocked C5b-9-mediated
7 hemolysis in 20 percent human serum," in
8 a particular concentration.
9 Q. Do you see the sentence right
10 after the citation to Figure 14 starting with
11 "Taken"?
12 A. Oh, I'm sorry:
13 "Taken together these experiments
14 indicated that unlike N19/8, which lost
15 half of its effectiveness at blocking
16 C5a generation upon being engineered as
17 an scFv, the 5G1.1 murine scFv retained
18 the capacity to block the generation of
19 both C5a and C5b-9."
20 Q. Right.
21 A. Yes, I see that.
22 Q. And is that surprising that N19/8
23 lost half its effectiveness when it was
24 engineered as an scFv?
25 MR. KNAUSS: Object to the form.

1 You may answer.
2 A. It's recognizing a different
3 epitope, has different binding affinity
4 properties. So the fact that its engineer is
5 an scFv, compared to the intact antibody or
6 the Fab, you know, it's more relevant to
7 compare the 5G1.1 scFv to the 5G1.1 native
8 antibody.
9 And that's what the beginning of
10 Column 50 indicates clearly, that the 5G1.1
11 scFv retained similar activity to that
12 apparent molecule. Right?
13 So I think that's a relevant
14 comparison. Comparing two different
15 antibodies with different epitopes and
16 different structures is not a relevant
17 comparison.
18 Q. The -- according to Evans, the
19 N19/8 scFv is an example of what happens when
20 you reengineer an antibody as an scFv, it
21 could affect its properties. Right?
22 A. I wouldn't generalize from that
23 one example, given all the examples we have
24 for the 5G1.1 scFvs and Fds and humanized
25 versions that all retain binding specificity.

1 So, you know, that particular
2 single case is not a generalizable
3 observation. In most cases, in fact, all the
4 cases I've encountered, scFvs behave in terms
5 of their binding affinity very much like Fabs
6 or intact antibodies.
7 MR. COCHRAN: All right. I think
8 we can probably break for lunch.
9 THE WITNESS: Great.
10 THE VIDEOGRAPHER: The time now
11 is 12:22 p.m. This concludes Media 3.
12 Off the record.
13 (Lunch recess taken from
14 12:22 p.m. to 1:08 p.m.)
15 (Continued on the next page.)
16 - - -
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1 A F T E R N O O N S E S S I O N
2 - - -
3 (Time noted: 1:08 p.m.)
4 - - -
5 THE VIDEOGRAPHER: The time now
6 is 1:08 p.m. This begins Media 4. On
7 the record.
8
9 J E F F R E Y R A V E T C H, resumed and
10 testified further as follows:
11 CONTINUED EXAMINATION
12 BY MR. COCHRAN:
13 Q. Welcome back.
14 A. Thank you.
15 (Ravetch Exhibit 22, US Patent
16 Application Publication Number
17 2003/0232972, marked for identification,
18 as of this date.)
19 Q. All right. We marked as
20 Exhibit 22 Patent Application Publication
21 Number 2003/0232972, first inventor Katherine
22 S. Bowdish.
23 Do you recognize this document,
24 sir?
25 A. Yes, I do.

1 Q. Do you rely on this document in
2 your declarations?
3 A. Yes, I do.
4 Q. Do you agree that a POSA would
5 have understood that the focus of Bowdish is
6 the generation of antibodies that have a
7 peptide of interest inserted into a CDR of an
8 antibody molecule so that the base antibody
9 would serve as a scaffold for presentation of
10 the peptide?
11 MR. KNAUSS: Object to the form.
12 But you can answer that,
13 Dr. Ravetch.
14 A. So in the summary of the
15 invention in Column 1, the inventors state
16 that:
17 "Provided herein are biologically
18 active recombinant antibodies and
19 fragments thereof that mimic the
20 activity of biologically active
21 peptides, methods of making such
22 antibodies, and methods for their use in
23 therapy and diagnosis."
24 Q. But the focus of Bowdish is to
25 insert a peptide of interest into a CDR region

1 of an antibody. Right?
2 MR. KNAUSS: Object to the form.
3 A. So that's one of the embodiments
4 found in Bowdish as a way of presenting
5 biologically active peptides to use the CDRs
6 of antibodies as a site for their insertion.
7 Q. And it was the peptide that had
8 the biological effect studied by Bowdish.
9 Right?
10 MR. KNAUSS: Objection, vague.
11 A. So the -- so once again, the
12 intention of Bowdish is to use a antibody, a
13 scaffold antibody, and by inserting a peptide
14 into a CDR region, for example, the activity
15 of that peptide can be presented to cells in
16 their biological context.
17 Q. Did it matter to Bowdish which
18 antibody was used as a scaffold?
19 MR. KNAUSS: Lacks foundation.
20 A. So I note that Bowdish is
21 associated with Alexion, and as such, the
22 antibody scaffold that Bowdish uses would be
23 one that would be available and accessible at
24 Alexion.
25 Q. Does Bowdish discuss the

1 treatment of complement-mediated conditions
2 such as PNH?
3 A. That does not appear to be the
4 intention of the patent application of
5 Bowdish.
6 Q. Was the --
7 A. The antibody is a scaffold, as we
8 discussed earlier, for the insertion of a
9 biologically active peptide.
10 Q. Was it the intention of Bowdish
11 to investigate anti-C5 antibodies?
12 MR. KNAUSS: Object to the form.
13 A. Well, he's investigating anti-C5
14 antibodies insofar as he's using an anti-C5
15 antibody as a scaffold for the insertion of a
16 particular peptide. So he is investigating
17 indirectly the antibody itself and its
18 structure, stability, and its biological
19 properties.
20 Q. The anti-C5 activity of the
21 antibody wasn't investigated by Bowdish.
22 Right?
23 A. No, and nor could it be, because
24 the region of the antibody that he's replacing
25 is the CDR3 of the heavy chain, which is

1 critical for the C5 binding activity.
2 Q. Do you agree that Bowdish does
3 not disclose the entire amino acid sequence
4 claimed by Sequence ID Numbers 2 and 4 of the
5 challenged patents?
6 A. I disagree.
7 Q. So in your opinion, Bowdish
8 discloses the entire amino acid sequence of
9 Sequence ID 2 and 4?
10 A. By virtue of Bowdish's explicit
11 incorporation by reference, the sequences from
12 the Evans publication, he is providing a
13 single reference with the complete sequences
14 that I was able to determine relate to the
15 Sequence ID 2 and 4.
16 Q. Right. We'll get that -- putting
17 aside Evans for now, can you tell me if
18 Bowdish alone, in the four corners within
19 Bowdish, discloses the entire amino acid
20 sequence of Sequence ID Numbers 2 and 4
21 claimed for the patents?
22 A. See --
23 MR. KNAUSS: Object to the form.
24 You can answer.
25 A. -- the problem I'm having with

1 your question, Counselor, is that I can't
2 ignore the explicit incorporation of the Evans
3 sequence, and in particular, since it's a CDR3
4 that Evans is -- is that Bowdish is replacing,
5 and Evans has only one CDR3 sequence. There
6 is no ambiguity as to what is being replaced.
7 So in my understanding of this
8 reference, the complete sequence is provided
9 to a POSA.
10 Q. So in order to get the complete
11 sequence claimed by the patents, you need
12 evidence. Right?
13 A. Bowdish clearly states that the
14 parent antibody is an antibody that has the
15 CDR3 found in Evans.
16 Q. So you need Evans to get the full
17 sequence of Sequence ID Numbers 2 and 4
18 claimed by the patents. Right?
19 A. But Evans is in Bowdish.
20 Q. But Bowdish does not disclose the
21 entire sequence?
22 A. Right. So I --
23 MR. KNAUSS: Asked and answered.
24 You can answer, Mr. Ravetch.
25 A. So the problem I'm having is

1 that, you know, it's been explained to me from
2 a legal standpoint that when one incorporates
3 by reference, the entire reference is part of
4 the four corners of the patent.
5 So from that perspective, Bowdish
6 includes the CDR3 sequence of Evans. And I
7 don't, I guess, understand the distinction
8 between that and saying that the sequence is
9 not explicitly disclosed because it is
10 explicitly disclosed. You know exactly what's
11 been removed, and you know exactly what used
12 to be there.
13 Q. Let's go to Figures 13A and 13B
14 of Bowdish. Figures 13A and 13B show Sequence
15 ID Numbers 67 and 69 -- right? -- among two
16 others?
17 A. Yes, correct.
18 Q. And Figure 13A says that Sequence
19 ID Number 67 is the 5G1.1 heavy chain. Right?
20 MR. KNAUSS: Object to the form.
21 Q. With the TPO mimetic in it.
22 Right?
23 A. So Figure 13A depicts the amino
24 acid sequence of the 5G1.1/TPO heavy chain,
25 SEQ ID Number 67.

1 Q. And other than the TPO mimetic,
2 that's the amino acid sequence from Evans.
3 Right?
4 MR. KNAUSS: Object to the form.
5 A. Excluding the leader sequence, of
6 course, and the linker sequence found in
7 Evans, the CDR -- the framework regions align
8 with, and CDR sequences will align with Evans,
9 with the exception of the CDR3, the heavy
10 chain.
11 Q. And the 5G1.1 referenced here in
12 Figure 13 of Bowdish is the murine sequence.
13 Right?
14 A. No, that's not correct. It's the
15 humanized 5G1.1 sequence.
16 Q. How do you know that?
17 A. You know that from the alignment
18 with Evans that we just discussed.
19 Q. So you had to do the alignment to
20 make sure it was humanized?
21 A. As I said, it would be routine
22 for one of skill in the art, when looking at a
23 sequence, to run it through the standard
24 sequence hemology database, and it would be
25 apparent instantly that the frameworks are

1 human derived and the CDRs are not human
2 derived, and that would tell us that it's the
3 framework humanized antibody sequence.
4 Q. You wouldn't know that just from
5 looking at the sequence, though. Right?
6 A. That's not the way a skilled
7 scientist would approach the information
8 contained in a protein sequence.
9 Q. So that's not really an answer to
10 my question. You wouldn't know that
11 information just by looking at the sequence
12 disclosed in Bowdish. Right?
13 A. You would know that information
14 by looking at the sequence disclosed in
15 Bowdish because you would compare it to
16 sequences in the database.
17 Scientists do not routinely
18 memorize thousands of sequences, so -- but we
19 have the tools to allow us to analyze it
20 quickly without any ambiguity to determine
21 what the sequence would be.
22 Q. And what are some of the reasons
23 why you would analyze the sequence in the way
24 you just described?
25 A. Because once again, going back to

1 the Bell disclosure, that the eculizumab is a
2 humanized 5G1.1 antibody, you would be
3 motivated to look at the eculizumab references
4 as well as the 5G1.1 references, and you would
5 find Bowdish quite readily by doing that.
6 And then, using the Bowdish
7 information, you would determine that, in
8 fact, Bowdish aligns, as he explains in the
9 specification, or she explains in the
10 specification -- excuse me -- aligns with the
11 Evans sequence which a humanized 5G1.1.
12 So as a POSA in 2007 approaches a
13 question of what is the sequence of
14 eculizumab, what's available to the POSA would
15 be the information provided in Bell and the
16 motivation from Bell to then pursue the
17 analysis that leads you, inexorably, to
18 Bowdish as well as Evans, and Tacken as well,
19 for example.
20 Q. So in your opinion, you're -- a
21 POSA in 2007 is starting with the question,
22 what is the sequence of eculizumab? Right?
23 A. A POSA would be motivated to
24 generate eculizumab as a molecule for the
25 purposes of treatment of PNH.

1 Q. Why?
2 A. Because of the disclosure in
3 Bell, and Hill and Hillmen, but Bell in
4 particular, because it is effective at the
5 treatment of PNH.
6 Q. So a POSA would be motivated to
7 seek out the sequence of the antibody that was
8 shown to be effective in the treatment of PNH.
9 Right?
10 A. Yes.
11 Q. And a POSA would be led down the
12 path of what the references told the POSA.
13 Right?
14 MR. KNAUSS: Object to the form.
15 A. What the references told the POSA
16 and the POSA's own ability to use the
17 information provided in those references to
18 find analogous references.
19 So while Tacken might not be
20 directly referenced in Bell, Tacken talks
21 about eculizumab and a 5G1.1 humanized
22 sequence.
23 A POSA would find that readily
24 because -- and it's, of course, an
25 Alexion-supported study with Alexion

1 scientists, so you would have all that
2 information that would lead you to these
3 various references.
4 Q. And the goal that you would have
5 in mind while being led down these various
6 references would be determining the sequence
7 of eculizumab now. Right?
8 A. To --
9 MR. KNAUSS: Asked and answered.
10 You may answer.
11 A. Yeah, to determine, or to have a
12 method of producing eculizumab. And to do
13 that, you would need the sequence to be able
14 to express it recombinantly, which is a fairly
15 standard procedure in 2007.
16 (Discussion off the record.)
17 Q. Let's go back to Bowdish Figures
18 13A and 13B. And looking at the page, it
19 doesn't have an "h" in front of 5G1.1. Right?
20 A. That's correct.
21 Q. And that's correct for 13B as
22 well?
23 A. That's correct.
24 Q. And neither 13A nor 13B mention
25 "human" anywhere. Right?

1 A. Not in this figure.
2 Q. Does Bowdish mention that 5G1.1
3 is humanized anywhere else within Bowdish?
4 A. (Document review.)
5 So in paragraph 19 -- Column 19,
6 paragraph 192, it describes the analysis of
7 the purified 5G1.1+peptide antibody, which is
8 disclosed in Figure 13A and 13B. And it says
9 that:
10 "The FACS staining was performed
11 essentially as described previously
12 herein, with the exception that the
13 detection was done using PE conjugated
14 F(ab')2 fragment of goat anti-human
15 IgG."
16 So that tells us right away that
17 the sequences being used in Bowdish are human
18 in nature, otherwise this detected antibody
19 would have been anti-mouse.
20 Q. But other than that assay, it's
21 the only thing in Bowdish that a POSA would
22 look to -- strike that question.
23 The FACS staining in Bowdish is
24 the only thing that hints at the sequences in
25 13A and B are human. Right?

1 A. It's not hinting.
2 MR. KNAUSS: Object to the form.
3 You can answer.
4 A. It's not hinting, Counselor.
5 It's explicit. You know, any POSA reading
6 that would know immediately that the 5G1.1 is
7 a human sequence. And then the reference to
8 Evans would direct a POSA directly to the
9 humanized sequences of Evans.
10 So there would be no ambiguity
11 that we're looking at a murine sequence,
12 otherwise the assay would make no sense and
13 the experiment would have been a failure.
14 Q. But Tacken -- sorry -- Bowdish
15 doesn't, in 13A and B, doesn't say that the
16 sequences are human. Right?
17 A. It doesn't have to. He's giving
18 a POSA the information that would inform a
19 POSA that this is a human sequence. And Evans
20 is incorporated by reference, and Evans has
21 nine examples of human sequences.
22 So it would be very clear that
23 this is a human sequence that we're dealing
24 with, and since the only part of the sequence
25 that has been replaced is a CDR3, and all

1 examples of CDR3s in those nine examples are
2 the same, it becomes a very straightforward
3 analysis to combine those to derive the
4 starting antibody that Bowdish began with
5 before replacing CDR3 with the TPO mimetic
6 peptide.
7 Q. Does Bowdish say "eculizumab"?
8 A. No, she does not.
9 Q. Bowdish does refer to 5G1.1.
10 Right?
11 A. That's correct.
12 Q. And your opinion, a POSA looking
13 for the sequence of eculizumab would be led to
14 Bowdish because of its reference to 5G1.1?
15 A. And the fact that the
16 investigators are from Alexion. Right? And
17 that is the company associated with
18 eculizumab. Right? So that's another
19 direction that a POSA would take in trying to
20 identify the 5G1.1 eculizumab sequence.
21 Q. Where would a POSA go after
22 Bowdish?
23 MR. KNAUSS: Object to the form.
24 Go ahead and answer.
25 A. So Bowdish with Evans

1 incorporated is, from my analysis,
2 anticipatory. Everything you need is found in
3 Bowdish for the sequences found in the claims
4 2 and 4, Sequence ID 2 and 4. Right? So
5 Bowdish, in light of -- or incorporating
6 Evans, is complete in itself.
7 Q. Go no further than Bowdish
8 itself?
9 MR. KNAUSS: Object to the form.
10 Asked and answered.
11 A. Right. In order to -- in my
12 anticipation of our analysis, which is on the
13 '149 Patent, not in the other patents but in
14 the '149 Patent, where the only claim is to a
15 claim to a sequence for that antibody, there,
16 "an antibody that binds C5 comprising a heavy
17 chain consisting of SEQ ID 2 and a light chain
18 consisting of SEQ ID Number 4," Bowdish will
19 anticipate, from my analysis, that claim.
20 Now, as I've also said in my
21 declaration, there are other routes to obtain
22 the sequences for eculizumab, SEQ ID 2 and SEQ
23 ID 4, that would render the claim obvious as
24 well. And those are different grounds that
25 I've shown.

1 But if you ask me is Bowdish
2 alone sufficient to anticipate the claim of
3 the '149 Patent, the answer is yes.
4 Q. And you agree --
5 A. That's my opinion.
6 Q. And you agree that Bowdish
7 incorporates Evans for the process for
8 creation of the 5G1.1 antibody. Right?
9 A. That's what's stated in the
10 Patent:
11 "Construction of 5G1.1 is
12 described in US Application Serial
13 Number 08/487,283 incorporated herein by
14 reference."
15 Q. Okay. And there's no "h" in
16 front of that 5. Right?
17 A. It doesn't have to be. We know
18 that's human.
19 Q. Well, going back -- it's going
20 back to Evans, though. Right?
21 A. No. I'm sorry.
22 MR. KNAUSS: Object to the form.
23 The question is not clear. Can
24 you just ask the question clearly,
25 please?

1 Q. Okay. Paragraph 191 in Bowdish.
2 Second sentence:
3 "Construction of 5G1.1 is
4 described in U.S. Application Serial
5 Number 08/487,283, incorporated herein
6 by reference."
7 Right?
8 A. That's what it says.
9 Q. How do you know that's the Evans
10 Patent?
11 A. (Document review.)
12 I need to look at the Evans
13 Patent. Excuse me. Thank you. Looking at
14 the wrong Patent.
15 On the face page of the Evans
16 Patent, it says "Application
17 Number 08/487,283."
18 Q. You don't cite to the '283
19 application in your declaration. Right?
20 A. I cite --
21 MR. KNAUSS: Objection to form.
22 A. I cite to the '245 Patent.
23 Q. Not to the application. Right?
24 MR. KNAUSS: Object to the form.
25 A. I believe it's the same.

1 Q. And which 5G1.1 is Bowdish
2 referring to here in this sentence?
3 A. There's -- well, in Bowdish
4 there's only one 5G1.1, and he describes the
5 sequences in Figure 13A and 13B. And as we've
6 said, when one then reviews the entirety of
7 the Patent, one sees that those sequences must
8 be human by two criteria; one, by the use of a
9 secondary antibody that only recognizes human
10 antibody, and by a simple sequence alignment
11 that a POSA would routinely carry out when
12 looking at a sequence.
13 Q. Sticking strictly with this
14 sentence here, "construction of 5G1.1," and
15 then it incorporates Evans, which 5G1.1 is
16 Bowdish referring to for the "construction of
17 5G1.1"?
18 MR. KNAUSS: Asked and answered.
19 A. Once again, he's referring to the
20 5G1.1 humanized sequences described in the
21 '245 Patent.
22 Q. This sentence doesn't say
23 anything about being human. Right?
24 A. Counselor, it's not necessary if
25 the experiment tells you that it's human. I

1 mean, I believe any POSA will read the
2 entirety of the Patent and not just one line,
3 and try to determine what 5G1.1 they're
4 referring to.
5 The '245 Patent, as you correctly
6 point out, has both murine as well as
7 humanized sequences. However, given the full
8 disclosure of this specification and the
9 routine knowledge a POSA would have for
10 sequence analysis, there would be no ambiguity
11 that they're referring to the humanized
12 sequences in this Patent.
13 Q. So the last sentence of paragraph
14 191 in Bowdish states "The 5G1+peptide was
15 produced as a whole IgG antibody." Right?
16 A. That's what it states.
17 Q. (Reading): "See Figures 13A and
18 13B"?
19 A. Correct.
20 Q. It doesn't say what isotype that
21 IgG is. Right?
22 A. A POSA looking at those sequences
23 would immediately recognize the fact that they
24 are hybrid isotype -- subclasses.
25 Q. By eye?

1 A. Actually, you could do it by eye,
2 and I've actually shown the analysis by eye,
3 because there's a distinctive sequence of the
4 hinge regions between the G2 and G4 sequences.
5 So one can do it by eye if you're
6 a POSA familiar with antibody sequences.
7 Those are very distinctive hinge regions.
8 But it wouldn't be necessary.
9 Like I said, we don't have to memorize
10 thousands of sequences. We have a simple
11 device called a computer which allows us to
12 screen very rapidly and tell us immediately
13 what the sequences relate to.
14 Q. Bowdish doesn't disclose that
15 it's a hybrid construct. Right?
16 A. No, he --
17 MR. KNAUSS: Asked and answered.
18 A. No, he does, explicitly, in SEQ
19 ID 67.
20 Q. Because you can, by your eye, see
21 that it's a hybrid sequence?
22 A. Among other ways of knowing, he
23 discloses a sequence which any POSA would look
24 at, compare it to sequences in the database,
25 and be able to determine immediately that it

1 was not either a G2 or a G4 but a hybrid
2 G2/G4.
3 Q. There's no language used within
4 Bowdish itself that says that sequences in
5 Figures 13A and B are hybrid G2/G4 sequences?
6 A. Right. So there would -- it's my
7 understanding that you don't have to disclose
8 information in patents that are routine to a
9 POSA. And this is routine to a POSA. So, you
10 know, why belabor the effort in the Patent
11 office, providing unnecessary information?
12 The information is all here for a POSA to
13 appreciate.
14 Q. It wasn't quite my question, sir.
15 It's just: Does Bowdish say
16 anywhere, using words, that the sequences
17 disclosed in Figures 13A and B are hybrid
18 sequences?
19 A. He discloses it using letters.
20 Q. And he discloses it using the
21 amino acid one-letter code. Right?
22 A. The amino acid one-letter code to
23 a POSA are words that we understand and can
24 decode.
25 Q. Other than that, there's nowhere

1 else in Bowdish that says that those sequences
2 are hybrid sequences. Right?
3 A. I don't understand the question.
4 I've answered --
5 Q. Putting aside your eyeballing of
6 Figures 13A and B --
7 A. That's not what I said,
8 Counselor.
9 MR. KNAUSS: Let him finish the
10 question, Dr. Ravetch, before you
11 answer.
12 Q. -- there's nowhere in Bowdish
13 that says that those sequences are hybrid
14 sequences. Right?
15 A. First of all, I did not say you
16 could eyeball the sequences. That's one way
17 to do it. I can do it. I've been looking at
18 these sequences for a long time.
19 A POSA, you know, would use a
20 simple sequence comparison to identify those
21 sequences. So that's the first correction I'd
22 like to make.
23 Secondly, the words "G2/G4" are
24 unnecessary and superfluous given the
25 information contained in SEQ ID -- Figures 13A

1 and 13B.
2 So if you're asking do the actual
3 English words say "G2/G4," my answer is it's
4 unnecessary and superfluous.
5 Q. So then your answer is no, it
6 does not say "G2/G4"?
7 A. My answer is what my answer is.
8 It's superfluous.
9 Q. Can you go to paragraph 83 of
10 your declaration? I'm in the one for the '880
11 Patent.
12 So here in paragraph 83 of your
13 declaration, you say:
14 "A POSA would have easily
15 determined that the sequences shown in
16 Figures 13A and 13B of Bowdish are
17 humanized 5G1.1 with a hybrid IgG2/IgG4
18 heavy chain, which would match with what
19 was expected for eculizumab."
20 Right?
21 A. That's what it says, yes.
22 Q. Why was that expected for
23 eculizumab?
24 A. Tacken explicitly tells us that
25 eculizumab is a humanized 5G1.1 with a hybrid

1 G2/G4 heavy chain.
2 Q. But Tacken came after Bowdish.
3 Right?
4 A. I'd have to look at the dates to
5 confirm that, but they're certainly before the
6 2007 priority date. So from that point of
7 view, the analysis I carried out for a POSA as
8 of 2007, the -- they're both prior art.
9 Q. So in your opinion, from Tacken
10 and looking backwards to Bowdish, you would
11 know that the sequences disclosed in
12 Figures 13A and B were a hybrid sequence?
13 A. I wouldn't say I'm looking
14 backwards at Bowdish. Bowdish stands alone
15 for the 5G1.1 sequence that she discloses.
16 And the complete sequence for the
17 5G1.1, which I state can be determined to be a
18 G2/G4 hybrid, we also have, you know, Tacken
19 referring to Mueller, which gives us some more
20 information about the G2/G4 hybrid sequence
21 that was incorporated into the eculizumab
22 antibody.
23 So I think the combination was
24 one that would be readily apparent, that the
25 sequences provided in Bowdish with the CDR3

1 coming from the parent antibody in Evans have
2 all the features that would be expected for
3 eculizumab.
4 Q. In paragraph 83 of your
5 declaration, you don't cite Tacken here, do
6 you?
7 A. This is a summary of the prior
8 art discussing Bowdish in that paragraph.
9 When I discuss the grounds for obviousness
10 later on, I discuss it in, when appropriate,
11 in the context of Tacken as well.
12 So in Ground 2, for example, I
13 talk about Claim 2 is obvious over Bowdish and
14 Evans in view of Bell, Tacken, and Mueller.
15 But in a -- in the description of Bowdish, I'm
16 talking about Bowdish. Later on, I talk about
17 Tacken in paragraph 98 from August 15, 2005,
18 priority date.
19 Q. All right. I'm going to take you
20 back to paragraph 83, though.
21 A. Yes.
22 Q. And you provide a cite for the
23 very last sentence in paragraph 83. Right?
24 A. Meaning Exhibit 1004?
25 Q. Yes.

1 A. Yes, I do cite to 1004.
2 Q. You do not provide a cite for the
3 first sentence in paragraph 83. Right?
4 A. (Document review.)
5 There's no cite listed there,
6 though I have explained that is discussed in
7 the discussion of Tacken. This is simply a
8 summary of the -- a brief summary, as I state,
9 of the prior art. It's not meant to be a
10 comprehensive summary of the prior art.
11 So my Bowdish description is a
12 brief description of Bowdish. Not everything
13 is included in that description. Similarly
14 with Tacken. But when I describe the grounds
15 for obviousness in light of Tacken, I describe
16 it in more detail.
17 Q. So also in that first sentence of
18 paragraph 83, you say:
19 "A POSA would have easily
20 determined that the sequences shown in
21 Figures 13A and 13B of Bowdish are
22 humanized 5G1.1."
23 Right?
24 A. That's correct.
25 Q. Why would a POSA have wanted to

1 do that?
2 A. Why would a POSA want to do that?
3 A POSA was motivated by the Bell reference,
4 for example, to determine the sequence of
5 eculizumab and would be directed to 5G1.1.
6 Bowdish incorporates 5G1.1 into
7 their study, and a POSA would discover the
8 5G1.1 and would want to determine is that a
9 human sequence or not, and could easily
10 determine that from sequence analysis and by
11 the disclosure in the Patent itself that it's
12 a human sequence.
13 Q. Does Bowdish's TPO mimetic
14 require a hybrid heavy chain as a scaffold?
15 MR. KNAUSS: Object to the form.
16 A. (Document review.)
17 I think Bowdish is silent on the
18 use of the particular Fc in this study. The
19 assays that are being done are in vitro cell
20 stimulation assays to interrogate the activity
21 of the TPO mimetic peptide.
22 Q. In your opinion, why would a POSA
23 be concerned with whether the amino acid
24 sequences in 13A and B are humanized?
25 MR. KNAUSS: Asked and answered.

1 A. Once again, from the Bell
2 disclosure, the eculizumab is identified as a
3 humanized 5G1.1 sequence, also known as
4 eculizumab, currently under development by
5 Alexion.
6 So a POSA is immediately pointed
7 to the fact that a humanized 5G1.1 sequence is
8 what is desired if you wanted to repeat the
9 studies shown in Bell.
10 So you would dismiss the murine
11 sequences. Once again, Bell is a clinical
12 study describing the results of the use of
13 eculizumab in PNH. As we discussed earlier,
14 murine antibodies are not appropriate to be
15 used in human clinical studies because of
16 their immunogenicity.
17 So for those reasons, clearly a
18 POSA would be motivated to look for humanized
19 5G1 sequences.
20 Q. Bell would motivate a POSA to
21 look for humanized sequences. Right?
22 A. Because Bell identifies humanized
23 5G1.1 as eculizumab. And that is the exercise
24 that I was charged with analyzing, whether a
25 POSA as of 2007 would have the motivation and

1 the ability to determine a sequence for
2 eculizumab.
3 Q. And Bell cites to Thomas. Right?
4 MR. KNAUSS: Asked and answered.
5 A. Bell cites to Evans. Bell also
6 cites to Thomas, but since we know that it's a
7 humanized sequence that has the properties
8 that we're discussing, the relevance of the
9 Thomas is only for the CDRs, and the Evans
10 sequence is the appropriate sequence. So
11 we've discussed that previously.
12 Q. Is there anything in Bowdish
13 itself that says that the sequences disclosed
14 in 13A and B bind to C5?
15 A. The reference to Evans is pretty
16 clear, because the Evans sequences all bind to
17 C5. So yes, by citing to Evans, Bowdish makes
18 it clear that this is the 5G1 that binds C5.
19 Q. Okay. And is it your opinion
20 that Bowdish and Evans disclose the exact same
21 amino acid sequences?
22 MR. KNAUSS: Objection, vague.
23 A. So once again, Evans describes
24 scFvs that are humanized in Example 11, nine
25 sequences of scFvs that are humanized.

1 Bowdish describes a full-length
2 intact antibody with a CDR3 that's been
3 substituted. It's otherwise, in the variable
4 domains, identical to the sequences found in
5 Evans for the variable domains.
6 Q. So then the sequences disclosed
7 in Evans -- strike that.
8 Aside from the CDRs, the
9 sequences disclosed in Evans and the sequences
10 disclosed in Bowdish are different. Right?
11 A. No.
12 MR. KNAUSS: Object to form.
13 A. No, that's not what I'm saying.
14 Maybe I'm not being clear.
15 (Document review.)
16 So Evans discloses a sequence
17 called human 5G1.1 scFv CO12. CO12. Right?
18 Right.
19 Q. Can you point to where you're
20 looking at?
21 A. I'm sorry. I'm on page 74 of
22 the '880 declaration. So that's one of the
23 nine humanized scFvs of 5G1.1 that are
24 disclosed in Evans. That sequence is a
25 humanized single-chain Fv with variable

1 domains for the heavy chain and light chain.
2 And the sequences of that, with
3 the exception of the CDR3, will match
4 perfectly to the Bowdish variable domains for
5 the light chain and heavy chain. And then the
6 missing sequence, or the starting sequence, is
7 provided by the CDR3 of Evans for that
8 sequence.
9 I think you can see a little bit
10 more clearly on page 80 the comparison that I
11 show between Bowdish, SEQ ID 69 and SEQ ID 67,
12 and the Evans 5G1.1 which is the scFv CO12.
13 And you see that the sequences align perfectly
14 with the exception of the CDR3 in Bowdish that
15 has been substituted with the TPO mimetic
16 peptide.
17 So it's the CDRs as well as the
18 humanized frameworks that are disclosed in
19 Evans that match the Bowdish sequence.
20 (Stenographer clarification.)
21 MR. KNAUSS: Would now be a good
22 time for a short break?
23 MR. COCHRAN: Sure.
24 THE VIDEOGRAPHER: The time now
25 is 2:10 p.m. This concludes Media 4.

1 Off the record.
2 (Recess taken from 2:10 p.m. to
3 2:24 p.m.)
4 THE VIDEOGRAPHER: The time now
5 is 2:24 p.m. This begins Media 5. On
6 the record.
7 (Ravetch Exhibit 23,
8 International Patent application,
9 publication Number WO 97/11971, first
10 inventor John P. Mueller, marked for
11 identification, as of this date.)
12 BY MR. COCHRAN:
13 Q. I've marked as Exhibit 23 a
14 International Patent Application Publication
15 Number WO 97/11971, first inventor John P.
16 Mueller.
17 Do you recognize this document,
18 sir?
19 A. Yes, I do.
20 Q. Do you rely on this document in
21 your declarations?
22 A. Yes, I do.
23 Q. Is it all right if I refer to
24 this as Mueller PCT?
25 A. Yes, that's fine.

1 Q. So Mueller PCT discusses
2 "Antibodies to porcine P-selecting protein,
3 porcine VCAM protein, and porcine CD86."
4 Right?
5 A. That's correct.
6 Q. That's not C5. Right?
7 A. That's not C5. No.
8 Q. All right. So keeping Mueller
9 PCT by your side, let's also go to your
10 declaration, the '880 one.
11 A. Yes.
12 Q. Page 67.
13 A. Yes.
14 Q. Paragraph 100.
15 A. Yes.
16 Q. In this paragraph, second
17 sentence, you say:
18 "Mueller PCT discloses the
19 sequence of eculizumab's hybrid
20 IgG2/IgG4 heavy chain."
21 Right?
22 A. Yes. Constant region, yes.
23 Q. Constant region?
24 A. Yes.
25 Q. Mueller doesn't mention the word

1 "eculizumab" though. Right?
2 A. He does not.
3 Q. If you were a POSA looking for
4 the sequence of eculizumab, how would you find
5 Mueller?
6 A. So on page 81 paragraph 127 of my
7 declaration, '880 declaration, I say:
8 "Tacken equates human 5Gl.l with
9 eculizumab, and calls it Alexion's
10 'potential product.' (EX1008 at 10.)
11 Tacken further teaches that eculizumab
12 contains an lgG2/G4 constant domain that
13 is the same as the human hybrid G2/G4
14 constant domain disclosed in its cited
15 reference 17, which is the Mueller 1997
16 article."
17 That's Exhibit 1008 at 11.
18 Q. So you're saying a POSA seeking
19 the sequence of eculizumab would find Mueller
20 because of Tacken?
21 A. That's correct. That's one way
22 he would find it. There's another way that a
23 POSA would find Mueller, and that comes from
24 Mueller's disclosure of an antibody, which
25 will sound familiar now, which is h5G1.1 CO12,

1 and that is shown, for example, with a hybrid
2 G2/G4 in Figure 15.
3 So a POSA looking for the human
4 5G1.1 would be directed to Tacken -- would be
5 directed to Tacken and would also be directed
6 to Mueller by virtue of their interest in the
7 human 5G1.1 sequence that is used as a control
8 in the Mueller reference -- Mueller PCT.
9 So the reference for that is on
10 page 12 lines 34 through 37. So it's:
11 "Figure 15: Flow cytometry of
12 human G4 mAb and human G2/G4 mAb binding
13 to U937 cells."
14 Right? And skipping down a few
15 lines, "h5G1.1 CO12 human G2/G4 mAb, or buffer"
16 we use as controls in that experiment.
17 Q. If we can go to paragraph 101 of
18 your '880 declaration, you state here that:
19 "Mueller PCT teaches development
20 of recombinant antibodies to reduce
21 immune-mediated organ transplant
22 rejection, including antibodies
23 comprising a hybrid IgG2/IgG4 constant
24 region."
25 Right?

1 A. That is correct.
2 Q. So that has nothing to do with
3 binding C5, though. Right?
4 MR. KNAUSS: Objection to form.
5 You, may answer.
6 A. Actually, it has to do with
7 whether the constant regions are going
8 activate the complement cascade or bind Fc
9 receptors.
10 So it's related to -- or -- it's
11 related to the development of antibody
12 therapeutics that would not activate an
13 inflammatory response through their Fc domain.
14 Q. But the recombinant antibodies
15 that Mueller discusses are not anti-C5
16 antibodies, are they?
17 A. That's correct.
18 MR. KNAUSS: Objection to form.
19 You can answer.
20 THE WITNESS: I'm sorry.
21 A. The Fabs of the antibodies, with
22 the exception of the control antibody, which
23 is the 5G1 antibody, are not anti-C5.
24 So Mueller discloses both
25 anti-VCAM antibodies. Right? Two of those

1 with the hybrid G2/G4 constant region. And as
2 a necessary control, he shows that an antibody
3 that does not bind to VCAM, but has the same
4 hybrid G2/G4, is not able to compete, and
5 therefore, is -- that antibody is the anti-C5
6 human 5G1.1.
7 Q. You agree that Mueller uses the
8 anti-C5 antibody as a negative control.
9 Right?
10 A. Well, he uses it for several
11 reasons. One is a negative control for the
12 Fab binding specificity. But he uses it as a
13 positive control to demonstrate that the
14 engagement of Fc receptors on U937 cells are
15 abrogated when one uses a G2/G4 hybrid Fc that
16 has the anti-C5 Fab on it.
17 Q. What are U937 cells?
18 A. Those are a myelomonocytic human
19 cell line that are used by investigators to
20 look at engagement of Fc receptors. They
21 express several of the Fc receptors.
22 And if one is, as Mueller was
23 aiming to do, develop a hybrid Fc that will
24 both reduce complement activation as well as
25 reduce Fc receptor activation, this is one way

1 you can assay for that.
2 Q. Why did Mueller want to do that?
3 MR. KNAUSS: Object to the form.
4 You may answer.
5 A. Right. So once again, Mueller's
6 motivation, as I said in 101, is the
7 development of recombinant antibodies to
8 reduce immune-mediated organ transplant
9 rejection.
10 So if you want to reduce immune
11 transplant rejection, you don't want to
12 activate mechanisms that will lead to
13 transplant rejection. The same way if you're
14 making antibodies that will prevent C5
15 activation, you don't want antibodies that
16 will induce C5 activation. So that's where
17 the two-entity antibody are required to be
18 considered.
19 Q. Page 12 of Mueller PCT.
20 A. Yes.
21 Q. The description in Figure 14. Do
22 you see that?
23 A. Yes.
24 Q. The second -- sorry -- third
25 sentence states:

1 "Results demonstrate the
2 recombinant ch3F4 HuG4 mAb does not
3 inhibit binding, whereas the recombinant
4 ch3F4 F(ab)2 inhibits binding."
5 Right?
6 A. Yes.
7 Q. And the binding that it's
8 speaking of is to the U937 cells. Right?
9 A. No, this experiment is talking
10 about the binding to the porcine aortic
11 endothelial cells. Right? So they're looking
12 at the Fab of the G4 intact antibody compared
13 to the F(ab')2 which lacks the Fc domain.
14 And what they observed is that in
15 one case it can inhibit binding to the porcine
16 aortic endothelial cells, and in the other
17 case they still see binding.
18 So the differences are the
19 presence or absence of an Fc domain, the G4 Fc
20 domain. They go on to state:
21 "This suggested that although the
22 ch3F4 G4 may have bound to the porcine
23 aortic endothelial cells, U937 cells
24 that adhere to the porcine aortic
25 endothelial cells through interaction of

1 the U937 cell FcR1 receptor with the
2 bound ch3F4 human G4 mAb."
3 So it's a ternary complex. So
4 instead of having just a cell and antibody, you
5 have cell, antibody, another cell. So they
6 want to remove the second cell from binding,
7 that's the U937 cell. And they've mapped that
8 binding presumptively to the Fc domain of the
9 G4 antibody.
10 Q. Right.
11 A. Yes.
12 Q. Because they did not want to
13 attract the U937 cells to the xenograft.
14 Right?
15 A. Well, no. That's just the --
16 it's the assay they're using. You know, the
17 assay is a surrogate for what might happen in
18 a clinical application. Right?
19 So in a clinical application, the
20 presence of an Fc receptor is not simply a
21 binding interaction, but it activates in some
22 cases the cells that are being bound. And if
23 they're macrophages or neutrophils, that can
24 lead to an inflammatory response.
25 So they're simply using this as a

1 surrogate assay to say it's worth eliminating
2 any potential for that type of interaction.
3 Q. Right.
4 A. So they then go on to say that:
5 "To eliminate this interaction,
6 chimeric antibodies containing the C1
7 and hinge of G2 and the C2 and C3 of G4
8 were constructed."
9 And that's the rationale behind
10 the G2/G4 that they've developed.
11 Q. Okay. So that rationale falls
12 within the context of Mueller's invention.
13 Right?
14 MR. KNAUSS: Object to form.
15 Sorry.
16 Q. Strike the question.
17 That rationale falls within the
18 context of Mueller's invention of improving
19 xenotransplantation rejection. Right?
20 MR. KNAUSS: Objection to the
21 form. You may answer.
22 A. No, I think it's more general
23 than that. It points to the motivation to
24 reduce any potential interaction of the Fc
25 with receptors that would potentially lead to

1 a inflammatory reaction. Right?
2 So whether it's complement
3 activation, Fc receptor activation, those were
4 undesirable in the context of transplantation
5 and in the context of treating inflammatory
6 diseases like PNH. So that was more generally
7 understood.
8 Q. Back to 11 of your '880
9 declaration. I'm sorry, what did I just say?
10 A. Paragraph 11?
11 Q. Paragraph 100.
12 A. Oh, 100. Okay.
13 Q. Back to paragraph 100 of
14 your '880 declaration, first sentence, you
15 state:
16 "Mueller PCT is an international
17 Patent application concerning the
18 same work described in the Mueller 1997
19 article that was published by Alexion."
20 A. That's correct.
21 Q. What do you mean by "same work"?
22 A. The same design of hybrid G2/G4
23 Fc domains to reduce binding to Fc receptors
24 and complement.
25 MR. COCHRAN: Let's go to Mueller

1 1997.
2 (Ravetch Exhibit 24, Mueller
3 1997, marked for identification, as of
4 this date.)
5 Q. So real quick, going back to
6 Mueller PCT.
7 A. Yes.
8 Q. I'm sorry to jump around.
9 Does Mueller PCT ever say that
10 the hybrid IgG2/G4 antibody still has activity
11 against C5?
12 A. (Document review.)
13 So Mueller refers, on page 12 in
14 Figure 15, to an antibody called h5G1.1 CO12.
15 And that's a unique identifier that would
16 direct a POSA to the Evans recombinant
17 antibodies. This is one of the antibodies,
18 it's under SEQ ID 20, and it's an antibody
19 that binds to C5.
20 Q. All right. But Evans doesn't
21 disclose a hybrid constant region. Right?
22 A. No, Evans discloses a scFv.
23 Right? So this is telling you that this is a
24 scFv sequence that's been associated with the
25 G2/G4 Fc. So that's the nomenclature which is

1 being used in that designation.
2 Q. There's nothing here in Mueller
3 PCT that says that that has retained any
4 activity against C5. Right?
5 A. Well, we know that human 5G1.1
6 CO12 retains binding to C5 from the Evans
7 publication.
8 Q. Right. Well, Evans said that the
9 scFv had anti-5 activity. Right?
10 A. Oh, yes. It has anti-5 activity
11 and you're asking: Does the addition of the
12 G2/G4 modify that?
13 Well, it's very clear from the
14 discussion that we looked at earlier that the
15 G2/G4 versus the G4 had no affect on epitope
16 binding specificity in Mueller, and it was not
17 expected to have any effect, if we recall
18 going back to the Thomas paper, where they say
19 you can contain avidity, but it's not going to
20 change binding specificity.
21 So this was known in the art that
22 a hybrid G2/G4 from Mueller's data did not
23 change binding specificity, and it would be
24 expected, certainly from Thomas' perspective
25 as well. So it was no surprise.

1 Q. But just to be precise, there's
2 nothing here in Mueller that says that this
3 specific antibody retains anti-C5 activity.
4 Right?
5 A. So this specific antibody, once
6 again going back to Tacken, is the antibody
7 that is a candidate for eculizumab. And we
8 know eculizumab retains binding to C5. So
9 Tacken calls out a human 5G1.1 G2/G4 as
10 eculizumab that binds C5.
11 Q. So because we know that
12 eculizumab has anti-C5 activity, we know that
13 this antibody in Mueller has anti-C5 activity.
14 Right?
15 A. In terms of the addition of the
16 G4/G2 hybrid sequence. But we know the G4
17 sequence has activity. Right? Thomas tells
18 us that. Thomas tells us that the Fc is not
19 going to influence the binding affinity or
20 specificity of the Fab.
21 Mueller shows us that for his two
22 anti-VCAM antibodies, that's true. There's no
23 difference in binding specificity. And Tacken
24 tells us very clearly that this antibody is
25 eculizumab.

1 So I think the prior art, as read
2 by a POSA in 2007, would really have a very
3 reasonable expectation that this antibody has
4 C5 binding activity.
5 Q. I'm going to Mueller 1997.
6 A. Yes.
7 Q. Did Mueller's studies start off
8 by looking at a G2/G4 hybrid?
9 MR. KNAUSS: Object to the form.
10 A. So Mueller's publication, like
11 the Mueller PCT, discusses the results of the
12 inhibition assay to the porcine aortic
13 endothelial cells and concludes that the
14 difference in binding between an F(ab')2 and
15 an intact antibody, G4 antibody, may be the
16 result of Fc receptor binding through the Fc
17 domain.
18 So that motivates Mueller in this
19 publication to create the G2/G4 hybrid
20 sequence, and what he says is that rather than
21 altering the specific -- sorry, I'm on page
22 446, the last paragraph on the right hand
23 column:
24 "Rather than altering the
25 specific residues known to mediate

1 complement fixation and FcR binding, we
2 explored the possibility of creating an
3 antibody with a composite human constant
4 region. To create chimeric mAbs which
5 would not activate complement or bind to
6 FcRs, we utilize the overall similarity
7 in the human G2 and G4 primary sequences
8 to design a human G2/G4 composite
9 antibody," and it describes what that
10 composite looks like.
11 And then it says:
12 "The resulting mAb did not
13 contain the antibody sequences necessary
14 for FcR binding, nor any epitopes that
15 would likely be immunogenic."
16 And then they did the experiment
17 we described, looking at what happens in the
18 U937 binding assay, and demonstrated as we saw
19 in Mueller PCT, that this hybrid didn't -- no
20 longer showed Fc receptor binding activity.
21 Q. You'll agree that Mueller started
22 out looking at IgG4 antibodies. Right?
23 MR. KNAUSS: Object to the form.
24 You may answer.
25 A. Right. The initial studies were

1 performed on the VCAM antibodies with G4 Fcs,
2 and then they recognized that they could
3 improve on that by making the hybrid G2/G4
4 hybrid sequences.
5 An alternative approach that they
6 discuss is making point mutations in the Fc
7 that had been described in the literature
8 prior to this date that would achieve the same
9 end.
10 Q. And Mueller was motivated to
11 improve the antibody in order to improve
12 xenograft rejections. Right?
13 MR. KNAUSS: Asked and answered.
14 A. No, this is a more general
15 statement to reduce Fc receptor binding as
16 well as complement activation. So he's
17 discussing it in the context of a generalized
18 Fc, like that had been published in the
19 literature before, using point mutations to
20 reduce Fc receptor binding activity.
21 (Stenographer clarification.)
22 Q. Let's go to paragraph 98 of your
23 '880 declaration. That's on page 66. This is
24 where you discuss Tacken. Right?
25 A. Right. Before doing that, can I

1 just make one addition to the last response
2 that I gave?
3 Q. Okay.
4 A. On page 451 of the Mueller
5 publication, he says --
6 (Stenographer clarification.)
7 A. He states:
8 "Additionally, the human G2/G4
9 antibody design should prove useful in
10 humanization of other antibodies
11 intended for human use, where
12 elimination of FcR binding and
13 complement activation may be desirable."
14 And that's the point I was making
15 earlier.
16 (Stenographer clarification.)
17 Q. So in paragraph 98 of your
18 declaration, you say:
19 "The first page of the Tacken
20 article also discloses that Alexion's
21 'potential product was studied' in the
22 underlying work."
23 Right?
24 A. That's correct.
25 Q. Let's look at Tacken.

1 (Ravetch Exhibit 25, Tacken
2 reference from Dr. Ravetch's
3 declaration, marked for identification,
4 as of this date.)
5 Q. In your opinion, what is
6 Alexion's "potential product" that was
7 referred to in Tacken?
8 A. Eculizumab.
9 Q. And how do you know that?
10 A. (Document review.)
11 Oh, I'm sorry for the delay.
12 It's in the footnotes. So it identifies three
13 of the authors:
14 "S.J.F., R.P.R., & D.W. are
15 employed by Alexion Pharmaceuticals
16 whose potential product was studied in
17 the present work."
18 Q. And that footnote doesn't mention
19 eculizumab. Right?
20 A. No, eculizumab is mentioned in
21 the statement on the next page, page 11, under
22 the paragraph "Recombinant antibodies."
23 (Reading):
24 "An isotype control antibody,
25 human 5Gi.1-mAb (5G1.1, eculizumab:

1 Alexion Pharmaceuticals) containing the
2 same G2/G4 constant region, is specific
3 for the terminal complement protein C5."
4 Q. And then how do you know that
5 that's the potential product that was
6 mentioned in the footnote?
7 A. I guess by reference to the, you
8 know, Bell and Hillmen, and Hill, which are
9 all clinical studies looking at eculizumab,
10 those are all Alexion studies. Alexion is
11 obviously developing -- was obviously
12 developing eculizumab as a potential
13 therapeutic product.
14 Q. Were they developing other
15 products?
16 A. I have no information about what
17 else they might have been developing, but
18 clearly eculizumab is cited here with the
19 Alexion authors as full disclosure, and we
20 know eculizumab is a product under clinical
21 development. That's made clear in Bell.
22 Q. And do you know if this potential
23 product that's referred to in the footnote
24 ever made it to market?
25 A. Eculizumab? As far as I

1 understand, eculizumab was marketed as
2 Soliris.
3 Q. So the -- it's your opinion that
4 this potential product referred to here in the
5 footnote could be nothing else besides
6 eculizumab?
7 A. I think the most reasonable
8 interpretation of what's in this study would
9 be that eculizumab, by the date of this
10 publication which is 2005, is a product that
11 is being developed at Alexion named eculizumab
12 that has anti-C5 activity. I think that's my
13 interpretation of this.
14 Q. And then going back down to page
15 11 where it mentions "5G1.1 eculizumab:
16 Alexion Pharmaceuticals," it doesn't say that
17 that's a potential product. Right?
18 A. It says what it does, that it's a
19 humanized antibody with the same G2/G4
20 constant region specific for the human
21 terminal complement component C5. It
22 identifies eculizumab, which we know from Bell
23 is the molecule being studied in PNH in phase
24 II studies, as well as in Hillmen and Hill.
25 Q. Okay. So -- but other than your

1 interpretation, there's nothing specific tying
2 those two together. Right?
3 A. I think it would be a stretch for
4 that not to be a case. To me, it's the most
5 parsimonious interpretation of what is meant
6 by this study.
7 Q. You mentioned in the footnote
8 that it refers to three of the authors?
9 A. That's correct.
10 Q. One of the authors it mentions is
11 Susan J. Faas?
12 A. Yes.
13 Q. The other author it mentions is
14 Dayang Wu. Right?
15 A. R.P.R. and D.W. R.P.R. is
16 Russell P. Rother, I believe. And D.W. would
17 be Dayang Wu.
18 Q. And among those three, only
19 Russell P. Rother is an inventor on the
20 challenged patents. Right?
21 A. I'd have to look at that again to
22 determine who the inventors are, listed
23 inventors on all the patents. But I'm
24 happy -- I have my binder. I can go look.
25 Q. Yeah, Why don't we take a quick

1 look.
2 A. Sure. So on the '149, he's
3 listed as an inventor.
4 Q. And let's stick with the '149.
5 Are Dayang Wu or Susan Faas listed as
6 inventors of the '149?
7 A. They are not.
8 On the '504, he's listed as an
9 inventor.
10 Q. And are Dayang Wu and Susan Faas
11 listed as inventors?
12 A. They are not.
13 On the '880, Rother is listed as
14 an inventor.
15 Q. And again, are Dayang Wu and
16 Susan Faas listed as inventors?
17 A. They are not.
18 And on the '189, Russell Rother
19 is listed as an inventor.
20 Q. And again, is Dayang Wu and Susan
21 Faas listed as inventors?
22 A. They are not.
23 Q. Let's go back to page 11 of
24 Tacken.
25 A. Yes.

1 Q. And that last sentence under the
2 heading "Recombinant Antibodies."
3 A. Mm-hmm.
4 Q. It refers to h5G1.1-mAb?
5 A. Yes.
6 Q. And 5G1.1. Those are the same
7 antibody. Right?
8 A. In the parentheses they define
9 that as eculizumab with a G2/G4 constant
10 region.
11 Q. That --
12 A. So I believe those -- that
13 nomenclature is interchangeable in this case.
14 Q. Okay. So --
15 A. In this specific case. I think
16 we've investigated in other publications that
17 the terminology is not necessarily consistent.
18 Here, the authors are being very
19 specific, telling us that the isotype control
20 antibody in this paper, h5G1.1-mAb, is
21 specifically eculizumab, Alexion, with the
22 G2/G4 constant region.
23 Q. So is it your testimony here
24 today that h5G1.1-mAb and 5G1.1 are the same
25 antibody?

1 MR. KNAUSS: Objection to form.
2 A. No. That's not my testimony.
3 I'm saying in this specific publication, those
4 terms are being identified as relating to the
5 eculizumab. It's not a general statement for
6 all uses of 5G1.1 or h5G1.1, because we know
7 that has been used in other publications with
8 different specificity. But here it's quite
9 explicit as to what the antibodies are
10 denoting.
11 Q. Is the h5G1.1-mAb referred to
12 here in Tacken a Fab fragment?
13 A. No, they say it's a -- it has the
14 same G2/G4 constant region. By definition,
15 that's not a Fab, that's an intact antibody.
16 Q. It cites to Reference 19 here.
17 Right?
18 A. Yes.
19 Q. What is Reference 19?
20 A. That's the Thomas reference.
21 Q. And earlier you were saying that
22 the h5G1.1-mAb was the Fab fragment in the
23 Thomas reference. Right?
24 MR. KNAUSS: Object to the form.
25 A. It may have been used in Thomas

1 as a Fab. I think here they're defining it
2 explicitly for the reader to tell you that
3 this is an intact antibody.
4 But more importantly, it's
5 defining what eculizumab is. And since these
6 are both inventors as well as employees of the
7 company, I think their characterization
8 carries a lot of weight.
9 Q. So is it your testimony that
10 there's only one eculizumab?
11 A. Yes.
12 Q. Is it your testimony that there
13 are different 5G1.1 antibodies?
14 A. So we've seen from the Evans
15 reference that there are nine humanized 5G1.1
16 sequences that are scFvs. We've seen in other
17 publications 5G1.1 denoted sometimes with an
18 "h" for human, with an "m" for mouse.
19 But if we follow the reasoning
20 within the stories, we can distinguish which
21 antibodies are which.
22 Q. And lead me through the reasoning
23 that you just mentioned.
24 A. So I went to the trouble to
25 actually resolve that in my declaration. So

1 looking, for example, at the '880, under the
2 section -- page 45, starting in paragraph 61,
3 "Eculizumab Development and Naming History."
4 I give a summary of the 5G1.1
5 development scheme and have a demonstrative on
6 page 50 which demonstrates the disclosures in
7 the prior art for the 5G1.1.
8 So starting in 1986, Thomas
9 describes h5G1.1 and also describes a human G4.
10 In 1997, we have Mueller in the PCT defining
11 "human 5G1.1 CO12 human G2/G4 mAb." In '97, we
12 have Mueller that we just discussed showing
13 "human 5G1.1 human G2/G4."
14 In 2002, Evans talks about
15 humanized 5G1, the scFv CO12. March of 2002,
16 we have the Alexion press release describing
17 Evans covering eculizumab.
18 December 2003, Bowdish refers to
19 5G1.1. We've just reviewed Bowdish 5G1.1 that
20 we understand has all the elements of the human
21 5G1.1 human G2/G4, with the exception of the
22 CDR3 which is found in Evans, and therefore, is
23 incorporated into that sequence.
24 August 2005, the Tacken reference
25 we're now looking at, talks about "human

1 5G1.1-mAb (eculizumab)" containing the "G2/G4
2 constant region." And then in September 2005,
3 Bell tells us that the human 5G1.1-mAb is
4 eculizumab.
5 So from these various
6 disclosures, we're able to construct a timeline
7 for the evolution of the name of 5G1.1 from a
8 murine sequence, to a humanized sequence, to a
9 full-length antibody, to full-length antibody
10 with a hybrid Fc domain.
11 Q. So there's an evolution of the
12 nomenclature for 5G1.1. Is that right?
13 A. Well, eventually, eculizumab is
14 the term that's adopted because that is the
15 required term based on the international
16 understanding, and eculizumab has elements
17 that tell us that it's a humanized antibody.
18 That's what the z-u indicates.
19 The l-i is for an
20 immunomodulatory molecule, e-c-u is their
21 proprietary discriminator, and "mab" stands
22 for an antibody, monoclonal antibody.
23 So eculizumab is the name that's
24 assigned to this molecule, and this molecule,
25 Tacken clearly demonstrates to us, is the

1 5G1.1 humanized antibody with the G2/G4
2 constant region.
3 Q. My question was a lot more
4 specific than that.
5 Are you saying that there was an
6 evolution of the nomenclature for 5G1.1?
7 A. I'm not sure --
8 MR. KNAUSS: Object to form.
9 A. I'm not sure I would use the term
10 "evolution." I would just say that there was
11 clarification of the use of 5G1.1 in the
12 literature, Thomas being the first publication
13 before Mueller, before the naming of
14 eculizumab.
15 Thomas is not going to use
16 eculizumab, obviously. It didn't exist as a
17 term. The G2/G4 hybrid doesn't come until we
18 get to the Mueller publication a year later.
19 So Mueller makes it clear that
20 the G2/G4 was a desirable aspect of an
21 antibody designed for therapeutic use in
22 humans when you want to minimize inappropriate
23 activation of inflammatory pathways. Right?
24 So I think this development
25 scheme is consistent with the understanding of

1 Tacken's 2005 summary.
2 Q. This summary doesn't cite to
3 Hill, does it?
4 A. So Hill describes this same
5 clinical trial as found in Hillmen and in
6 Bell. Right? And then Bell has an explicit
7 description of human 5G1.1 as eculizumab.
8 Right?
9 So Hill is not -- we talked about
10 that earlier, Hill and Hillmen are not going
11 beyond the clinical observations, and simply
12 say it's a humanized antibody against the C5
13 component.
14 MR. KNAUSS: Take a five-minute
15 break.
16 (Discussion off the record.)
17 THE VIDEOGRAPHER: The time is
18 3:24 p.m. This concludes Media 5. Off
19 the record.
20 (Recess taken from 3:24 p.m. to
21 3:42 p.m.)
22 THE VIDEOGRAPHER: The time now
23 is 3:42 p.m. This begins Media 6. On
24 the record.
25 BY MR. COCHRAN:

1 Q. Take you back to page 50 --
2 A. Yes.
3 Q. -- in your declaration, the
4 summary that we were just discussing.
5 A. Yes.
6 Q. Just to get back into it, notice
7 that Hillmen and Hill were not included in
8 this summary. Right?
9 A. They're not listed on here,
10 that's correct.
11 Q. You include Bell instead?
12 A. I include Bell, yes. He's on
13 this list in September 2005.
14 Q. And in your opinion, this summary
15 represents the name changes of 5G1.1 through
16 time. Right?
17 MR. KNAUSS: Object to the form.
18 A. I wouldn't call them name
19 changes, Counselor. I would refer to them as
20 clarifications of the eculizumab product from
21 the point of view of a POSA in 2007.
22 Q. And it starts with Thomas.
23 Right?
24 A. Thomas is the first reference
25 that lists 5G1.1, initially as a murine

1 antibody, and then as a humanized antibody, as
2 an Fab, and then as a G4 intact antibody. No
3 reference to eculizumab in Thomas.
4 Q. Right. And then the last two
5 references are Bell and Tacken. Right?
6 A. On this timeline, Bell and Tacken
7 are the last two, that's correct.
8 Q. And both Bell and Tacken cite
9 back to Thomas. Right?
10 A. Bell and Tacken -- well, Tacken
11 cites to Mueller and to Thomas. Bell cites to
12 Evans and to Thomas. So we have a series of
13 references.
14 Thomas, as I understand the way
15 the references are being used, Thomas is the
16 initiator of the program. Thomas is the first
17 monoclonal antibody that shows activity
18 against C5.
19 So if one is giving a scientific
20 overview of the development of a clinical
21 product like eculizumab, it's not
22 inappropriate to go back to the origins and
23 say, We started with a monoclonal antibody, a
24 mouse antibody. It had the activity and then
25 it was developed into a clinical product.

1 Q. But the antibody described in
2 Thomas was an undesirable antibody. Right?
3 MR. KNAUSS: Object to the form.
4 A. It depends what purposes they
5 were using it for. It was certainly quite
6 desirable for the analysis of the C5 pathway.
7 It's useful as a research tool, you know.
8 It's an important reagent, you know.
9 There were lots of aspects to
10 Thomas' murine antibody as a monoclonal, not
11 as a therapeutic to treat patients, but
12 certainly as an antibody that could be used.
13 I guess if you're treating mice, it's a
14 perfectly acceptable antibody.
15 Q. So in your opinion, there's
16 nothing in Thomas that suggested that the G4
17 anti-C5 antibody was promising for
18 therapeutics?
19 MR. KNAUSS: Object to the form.
20 A. So once again, as I said, the
21 activity of the Thomas study demonstrated that
22 you could inhibit C5 cleavage and inhibit both
23 C5a and b accumulation because other
24 antibodies didn't show that equivalent
25 activity. They were very biased to C5B and

1 not C5A.
2 It also showed you could spare C3
3 from being activated, from being blocked, C3
4 being very important in the mechanisms by
5 which immune complexes are retained in the
6 germinal center. They have roles beyond
7 inflammation in modulation of the immune
8 response.
9 So Thomas represented a strategy
10 that could lead to clinical products, but not
11 as a murine antibody. It required additional
12 engineering.
13 Q. Thomas disclosed to humanized --
14 A. What's that?
15 Q. Thomas disclosed to humanized --
16 A. Also discloses humanized. He
17 discloses a murine antibody and discloses
18 humanized antibodies as an Fab, yes.
19 Q. Let's take a -- let's go back to
20 Tacken real quick.
21 A. Sure.
22 Q. Tacken as a whole doesn't discuss
23 anything about treating PNH. Right?
24 A. That's correct. That's not the
25 purpose of Tacken.

1 Q. And Tacken as a whole doesn't
2 discuss anything about binding to C5. Right?
3 A. Beyond the citation to the
4 antibody and the fact that we know what
5 eculizumab activity is from Bell, for example,
6 it doesn't explicitly describe experiments
7 with 5G1.1 beyond use as a control antibody.
8 Q. And Tacken only mentions the word
9 "eculizumab" once. Right?
10 A. That's correct.
11 Q. And when it mentions eculizumab,
12 it cites to Thomas. Right?
13 A. It cites to Thomas. However, as
14 I said, the purpose of citing to Thomas is to
15 give background to the pathway, not to exclude
16 other publications that would be relevant to
17 eculizumab.
18 Q. And there's no reason for you to
19 think that that citation to Thomas is an
20 inaccurate citation. Right?
21 A. Well, it depends --
22 MR. KNAUSS: Objection to form.
23 You can answer.
24 A. It depends what it's being used
25 for. If it's being used to inform a reader of

1 this study that this is an antibody that was
2 initially developed as a monoclonal for the --
3 its ability to block C5 activation and C5
4 cleavage, that's perfectly fine.
5 But it's not being used to define
6 the structure of eculizumab because Thomas has
7 no reference to eculizumab. Thomas does not
8 use a G2/G4 hybrid Fc.
9 So one -- if -- any POSA who
10 would go to the Thomas reference would have no
11 confusion as to the fact that this is not
12 describing eculizumab.
13 Q. So where Tacken references
14 eculizumab and then cites to Thomas, in your
15 opinion, why doesn't Tacken cite to Mueller?
16 A. I can't answer on the part of the
17 authors as to why they made a certain
18 reference choice. I can simply explain how
19 that reference would be used by someone who
20 understands this particular field.
21 I think it would have been
22 appropriate to include other references beyond
23 Thomas, for example, in this citation,
24 including perhaps Mueller, including Bell.
25 But what was chosen here was

1 Thomas, and that's for you to ask the author
2 as to why he chose Thomas. I think it's a he,
3 isn't it? Yes, it's a he.
4 Q. So you believe Tacken cited
5 Thomas for background, but you don't know why
6 Thomas didn't cite Mueller?
7 A. That's fair. It is definitely
8 background. It definitely is where the story
9 starts, appropriately so, but it's not where
10 the story ends.
11 MR. KNAUSS: Object to the form
12 of the question.
13 Q. Let's find Bell again.
14 A. Sure.
15 (Discussion off the record.)
16 MR. KNAUSS: Here it is, 18.
17 THE WITNESS: Thank you. Yes,
18 Bell.
19 MR. COCHRAN: Excellent. Thank
20 you.
21 MR. KNAUSS: You're welcome.
22 Q. And also with Bell in hand now,
23 let's go to your '880 declaration?
24 A. Yes.
25 Q. Page 95, paragraph 148.

1 A. 148, yes.
2 Q. So in paragraph 148 of your '880
3 declaration, you say:
4 "Bell reports a Phase II clinical
5 trial in PNH patients that used
6 eculizumab in a dosing regimen with an
7 initial 600 mg dose phase given weekly
8 for four weeks followed by a maintenance
9 dose of 900 mg dose given bi-weekly."
10 Right?
11 A. Yes.
12 Q. And neither 600 nor 900 are 300.
13 Right?
14 A. 600 and 900 are divisible by 300,
15 but they are not 300.
16 Q. What else is 600 and 900
17 divisible by?
18 A. Certainly many other numbers.
19 However, in the case of a clinical product, we
20 like to minimize the number of vials that we
21 have to use in giving it to a patient.
22 We're doing a clinical trial
23 right now, and the fewer vials we can use, the
24 better for everyone. So if your dosing is 600
25 and 900, 300 would be the most reasonable

1 dosing a vial can use that gives you the least
2 amount of waste and the least amount of
3 potential contamination or loss of sterility.
4 Q. And what concentration would that
5 300 vial -- 300 mg vial be?
6 A. Well --
7 MR. KNAUSS: Object to the form.
8 A. -- the -- from other references
9 that I cite, the dose -- the concentration can
10 range from, you know, 1 milligram to 30
11 milligram per ml. Those are all disclosed.
12 Antibodies are often formulated
13 at about 10 mgs per ml, that's a pretty common
14 formulation, and I list a series of antibodies
15 that had been used at that concentration.
16 On page 96, we describe Campath
17 at 10 mgs per ml, for example, Herceptin,
18 Remicade, Rituximab, and so forth. So that's
19 not an uncommon concentration. It would be a
20 convenient concentration to have a 30 ml
21 solution if a 10 mg per ml concentration.
22 Q. And you agree that if you
23 formulated one antibody at a 10 mg
24 concentration, that it would work for another
25 one too. Right?

1 MR. KNAUSS: Object to the form.
2 A. No, that's not -- I mean, that's
3 not necessarily the case. But for clinical
4 studies that have been performed with
5 recombinant antibodies in a variety of
6 settings, that dose range seems to be
7 reasonable, and the publications that were
8 available prior to 2007 made it clear that
9 that's within the range that a POSA would
10 consider.
11 Q. So with any given antibody, you'd
12 have an expectation that you could concentrate
13 it at 10 mgs per ml. Right?
14 MR. KNAUSS: Object to the form.
15 A. I think that's not an
16 unreasonable assumption to, you know, given
17 what we know about how antibodies are purified
18 and how they're formulated. That's a
19 reasonable expectation.
20 And from my experience with
21 recombinant antibodies that are now being used
22 in clinical settings, that concentration was
23 easily attainable.
24 Q. You say here that Wang teaches
25 concentration ranges of 1 to 30 milligrams per

1 ml. Right?
2 A. That's correct.
3 Q. 10 is just one number in between
4 those two numbers. Right?
5 A. Wang basically provides that
6 whole range. You can use 1 mg per ml
7 concentration. It would require a lot more
8 vials, a lot more product to be potentially
9 wasted, and these are expensive drugs, so we
10 try to minimize waste in these drugs.
11 It's also harder to get a
12 complete filling of your syringe when you have
13 diluted antibodies. But it's not, you know,
14 uncommon to have lower concentrations for some
15 products, and it's -- some are a higher
16 concentration.
17 So shooting for a mid-range
18 concentration is a perfectly reasonable
19 approach to formulate an antibody.
20 Q. For example, you could use 20 mgs
21 per ml. Right?
22 A. You could use 20 mgs per ml. It
23 would be, you know, perhaps a less convenient
24 vialing schedule, but that could be used as
25 well. Basically Wang gives you the full

1 range.
2 Q. And you could use 25 mgs per ml
3 too. Right?
4 A. You could use 25 mgs per ml, and
5 once again, it's a question of minimizing
6 inconvenience to the pharmacy and to the
7 clinicians who are administering the drug.
8 Q. Other than convenience, there's
9 nothing else that points you to 10 mgs per ml
10 specifically, though. Right?
11 MR. KNAUSS: Object to the form.
12 A. I mean, you want single-use
13 dosage. That's an important consideration.
14 You don't want to go into the vial more than
15 once because of the issues related to
16 sterility and contamination.
17 So a formulation that gives you
18 300 milligrams, use once, discard the vial, is
19 certainly preferable than having a formulation
20 that gives you a larger volume that you then
21 have to use multiple times.
22 Q. Have you formulated antibodies
23 before?
24 A. Yes, I have.
25 Q. Are you concerned with

1 convenience when you formulate antibodies?
2 A. Yes, I am. And storage, you
3 know, if you need to store hundreds of vials
4 compared to only a few vials, it makes life a
5 lot easier.
6 Q. Dr. Ravetch, who drafted your
7 declarations?
8 A. I did.
9 Q. Did you have any help?
10 A. I was in discussion with counsel
11 during the drafting of my declaration. Drafts
12 were exchanged. I commented, made changes,
13 but the final product is one that I created.
14 Q. When you were retained by
15 counsel, what was the task that you were
16 given?
17 A. So the initial task, I think as
18 it is today, was to review the claims of the
19 various patents that we've been discussing,
20 the five patents, and to determine if, as of
21 2007, it would have been obvious or
22 anticipated for one of skill in the art to
23 develop evidence that the claims would be
24 anticipated or obvious.
25 Q. Did you do any searching

1 yourself?
2 A. Yes, I did.
3 Q. And what did you find?
4 A. Well, I searched in all kinds of
5 ways, looking at different aspects. I don't
6 recall precisely, but it's my typical approach
7 when starting on a case like this to review
8 the available literature as well as any
9 underlying literature that might be of
10 interest to me.
11 I don't necessarily keep notes of
12 that. It's just as ideas pop into my head, I
13 pull out references and look up particular
14 aspects. So that was something that I usually
15 do routinely.
16 Q. Of the -- strike that.
17 Did you find Tacken on your own?
18 A. Yes, as I said, I've been aware
19 of Tacken for a very long time.
20 Just to emphasis that point, if
21 we look at Tacken and look at Reference 4 of
22 Tacken, that's my publication. So I was very
23 much aware of Tacken because I've been aware
24 of this particular area for quite a while and
25 have made a lot of contributions in the area

1 of dendritic cell maturation and activation
2 and targeting antibodies to dendritic cells
3 and so on.
4 And that's still a focus of my
5 laboratory. We have developed antibodies that
6 activate dendritic cells in cancer patients,
7 leading to eradication of tumors through CD8
8 responses. So it's a very active area. So
9 yes, Tacken was one -- something I was aware
10 of for a very long time.
11 Q. Did you find Mueller in 1997 by
12 yourself?
13 A. Mueller in '97 was another
14 research article that I was aware of prior to
15 this litigation. And not uncommonly, I've
16 been interested in antibody Fc domains since
17 1982 when I cloned the first Fc receptors. So
18 it's been an area of active research for 40
19 years.
20 MR. COCHRAN: You know, I think
21 if we could take a five-minute break,
22 I'll look over my notes.
23 MR. KNAUSS: Sure.
24 THE VIDEOGRAPHER: The time is
25 4:07 p.m. This concludes Media 6. Off

1 the record.
2 (Recess taken from 4:07 p.m. to
3 4:19 p.m.)
4 THE VIDEOGRAPHER: The time now
5 is 4:19 p.m. This begins Media 7. On
6 the record.
7 BY MR. COCHRAN:
8 Q. Dr. Ravetch, can we go back to
9 paragraph 149 of your '880 declaration? This
10 is an page 96.
11 A. (Document review.)
12 Yes.
13 Q. You mentioned Dr. Ippoliti here?
14 A. I do.
15 Q. Who is Dr. Ippoliti?
16 A. Dr. Ippoliti is another expert in
17 this matter. I haven't met her with regard to
18 this -- these issues, but I have reviewed her
19 declaration.
20 Q. What are you relying on -- what
21 opinions of Dr. Ippoliti's are you relying on?
22 A. I'm not relying --
23 MR. KNAUSS: Objection,
24 overbroad.
25 THE WITNESS: Sorry.

1 MR. KNAUSS: Do your best to
2 answer.
3 A. Yeah, I'm not relying on
4 Dr. Ippoliti's opinions. I simply state that
5 they are consistent with my observations and
6 conclusions, and I say that she reaches
7 equivalent conclusions regarding obviousness
8 of these claim limitations for this and for
9 the other formulation claims.
10 MR. COCHRAN: Give me one minute.
11 I have no further questions.
12 MR. KNAUSS: So I need to do a
13 very brief redirect with just one issue.
14 Are you ready, Dr. Ravetch?
15 THE WITNESS: Yes.
16 EXAMINATION BY
17 MR. KNAUSS:
18 Q. I may have misheard you earlier
19 today, but did you testify at any point today
20 that the only anticipation, opinion, as
21 opposed to obviousness, that you have in this
22 case relates to the '149 patent?
23 A. I don't recall saying that but
24 that wouldn't be correct had I said that.
25 Q. Can you do me a favor, please,

1 and just turn to the table of contents of your
2 '880 declaration?
3 A. Yes.
4 Q. Do you see there recited a
5 heading for "Ground 1: Claim 2 is anticipated
6 by Bowdish" at page 71?
7 A. I do, yes.
8 Q. Can you just quickly page through
9 the opinions running from page 71 through page
10 77 that relate to Ground 1 and just let me
11 know when you're ready for a question.
12 A. (Document review.)
13 Yes.
14 Q. Okay. Sitting here today, do you
15 maintain the opinions as set forth in your
16 declaration on those pages that I just recited
17 to you?
18 A. Yes, I do.
19 (Continued on the next page.)
20
21
22
23
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25

1 MR. KNAUSS: Thank you. With
2 that, Dr. Ravetch, I have no further
3 questions.
4 THE WITNESS: Thank you.
5 THE VIDEOGRAPHER: Done? Off the
6 record?
7 MR. KNAUSS: Okay.
8 THE VIDEOGRAPHER: The time now
9 is 4:24 p.m. This concludes Media 7 of
10 7 of today's deposition. Off the
11 record.
12 (Time noted: 4:24 p.m.)
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1

2 A C K N O W L E D G M E N T

3

4 STATE OF)

5 : ss

6 COUNTY OF)

7

8 I, JEFFREY RAVETCH, hereby

9 certify that I have read the transcript

10 of my testimony taken under oath in my

11 deposition of February 23, 2024; that

12 the transcript is a true, complete, and

13 correct record of my testimony, and that

14 the answers on the record as given by me

15 are true and correct.

16

17 _____

18 JEFFREY RAVETCH

19

20 Signed and subscribed to

21 before me this _____

22 day of _____, 2024.

23 _____

24 Notary Public

25

1

2 C E R T I F I C A T E

3 STATE OF NEW YORK)

4 : ss.

5 COUNTY OF NASSAU)

6

7 I, PATRICIA A. BIDONDE, a Notary

8 Public within and for the State of New

9 York, do hereby certify:

10 That JEFFREY RAVETCH, the witness

11 whose deposition is hereinbefore set

12 forth, was duly sworn by me, and that

13 such deposition is a true record of the

14 testimony given by the witness.

15 I further certify that I am not

16 related to any of the parties to this

17 action by blood or marriage, and that I

18 am in no way interested in the outcome

19 of this matter.

20 IN WITNESS WHEREOF, I have

21 hereunto set my hand this day,

22 February 26, 2024.

23 _____

PATRICIA A. BIDONDE

24 Stenographer

Registered Professional Reporter

25 Realtime Certified Reporter

1 I N D E X

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2 Examinations		
MR. COCHRAN	6	16
3 MR. KNAUSS	209	16

4 E X H I B I T S

5 Ravetch		Page	Line
6 Exhibit 1	US Patent Number		
7	9,732,149 B2	9	7
8 Exhibit 2	US Patent Number		
9	9,725,504 B2	9	10
10 Exhibit 3	US Patent Number		
11	9,718,880 B2	9	13
12 Exhibit 4	US Patent Number		
13	10,590,189 B2	9	16
14 Exhibit 5	US Patent Number		
15	10,703,809 B1	9	19
16 Exhibit 6	Ravetch Declaration in		
17	Support of Petition in		
18	IPR2023-00933	9	22
19 Exhibit 7	Ravetch Declaration in		
20	Support of Petition in		
21	IPR2023-00999	10	1
22 Exhibit 8	Ravetch Declaration in		
23	Support of Petition in		
24	IPR2023-00998	10	5

25

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2 Page Line

3 Exhibit 9 Ravetch Declaration in
4 Support of Petition in
5 IPR2023-01069.....10 9
6 Exhibit 10 Ravetch Declaration in
7 Support of Petition in
8 IPR2023-01070.....10 13
9 Exhibit 11 Commercial antibody
10 sequence.....18 18
11 Exhibit 12 Declaration of Arturo
12 Casadevall for Patent
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20 Exhibit 15 Declaration of Arturo
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3 Exhibit 16 Declaration of Arturo
4 Casadevall for Patent
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6 Exhibit 17 "Inhibition of
7 complement activity by
8 humanized anti-C5
9 antibody and
10 single-chain Fv" by
11 Thomas et al.....63 23
12 Exhibit 18 Bell Patent Application
13 Publication Number US
14 2005/0191298.....89 23
15 Exhibit 19 Reference by Anita Hill
16 et al. titled "Sustained
17 response and long-term
18 safety of eculizumab and
19 paroxysmal nocturnal
20 hemoglobinuria" from
21 2005.....99 14

22

23

24

25

1 I N D E X

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3 Exhibit 20 "Effect of Eculizumab on
4 Hemolysis and
5 Transfusion Requirements
6 in Patients with
7 Paroxysmal Nocturnal
8 Hemoglobinuria" by Peter
9 Hillmen et al.....103 20
10 Exhibit 21 US Patent Number
11 6,355,245 B1.....115 21
12 Exhibit 22 US Patent Application
13 Publication Number
14 2003/0232972.....131 15
15 Exhibit 23 International Patent
16 application, publication
17 Number WO 97/11971,
18 first inventor John P.
19 Mueller.....163 8
20 Exhibit 24 Mueller 1997.....174 2
21 Exhibit 25 Tacken reference from
22 Dr. Ravetch's
23 declaration.....181 1

24

25 - - -

1 E R R A T A

2 INSTRUCTIONS TO WITNESS

3

4 Please read your deposition over

5 carefully and make any necessary corrections. You

6 should state the reason in the appropriate space

7 on the errata sheet for any corrections that are

8 made.

9 After doing so, please sign the errata

10 sheet and date it.

11 You are signing same subject to the

12 changes you have noted on the errata sheet, which

13 will be attached to your deposition.

14 It is imperative that you return the

15 original errata sheet to the deposing attorney

16 within thirty (30) days of receipt of the

17 deposition transcript by you. If you fail to do

18 so, the deposition transcript may be deemed to be

19 accurate and may be used in court.

20

21

22

23

24

25

1 E R R A T A

2 ERRATA SHEET FOR THE TRANSCRIPT OF:

3 Case Name: Samsung v Alexion

4 Dep Date: February 23, 2024

5 Deponent: Jeffrey Ravetch

Pg.	Ln.	Now Reads	Should Read	Reason
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1 E R R A T A (Continued)

Pg.	Ln.	Now Reads	Should Read	Reason
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_____

Jeffrey Ravetch

Signed and subscribed to before me

this ____ day of _____, 2024

_____

Notary Public

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