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Transcript of Aaron E. Miller, M.D.

Date: May 13, 2024
Case: Hopewell Pharma Ventures, Inc. -v- Merck Serono, S.A. (PTAB)

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Merck 2079
Hopewell v Merck
IPR2023-00480

WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

1 UNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD
3 _____
4 HOPEWELL PHARMA VENTURES, INC.,
5 Petitioner,
6 v.
7 MERCK SERONO S.A.,
8 Patent Owner.
9 _____
10 IPR2023-00480 (Patent 7,713,947 B2)
11 IPR2023-00481 (Patent 8,377,903 B2)
12
13 DEPOSITION OF
14 AARON E. MILLER, M.D.
15 New York, New York
16 Monday, May 13, 2024
17 8:59 A.M. EDT
18
19
20 Job No.: 534693
21 Pages: 1 - 192
22 Reported by: Monique Vouthouris, CCR, RPR, CRR

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4 Deposition of AARON E. MILLER, M.D., held at:
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6
7 NEW YORK HILTON MIDTOWN
8 1335 6th Avenue
9 New York, New York 10019
10
11
12 Pursuant to notice, before Monique Vouthouris,
13 Certified Court Reporter, Register Professional
14 Reporter, Certified Realtime Reporter, and Notary
15 Public in and for the States of New York and New
16 Jersey.
17
18
19
20
21
22

1 A P P E A R A N C E S
2
3 ON BEHALF OF PETITIONER
4 HOPEWELL PHARMA VENTURES, INC.:
5 ELDORA L. ELLISON, PH.D., ESQ.
6 OLGA A. PARTINGTON, PH.D., ESQ. (Via Zoom)
7 STERNE KESSLER GOLDSTEIN & FOX, PLLC
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9 Washington, D.C. 20005
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11
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18 New York, New York 10007
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1 ALSO PRESENT:
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3 Corporate Patent Counsel, Merck
4 HAROLD RODRIGUEZ, Planet Depos Technician
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C O N T E N T S

EXAMINATION OF AARON E. MILLER, M.D. PAGE
By Dr. Kan 7
By Dr. Ellison 189

E X H I B I T S

(Attached to transcript.)

MILLER DEPOSITION EXHIBIT PAGE
Exhibit 2077 Excerpt from "Primer on Multiple Sclerosis," by Barbara S. Giesser, "Issues in the Design and Interpretation of Multiple Sclerosis Clinical Trials." 99
Exhibit 2078 Article from Multiple Sclerosis Journal "Multiple sclerosis should be treated using a step-down strategy rather than a step-up strategy," by Aaron E. Miller, M.D. 136

1 PREVIOUSLY MARKED EXHIBITS

2 EXHIBIT NUMBER PAGE

3 1002.....14
4 1013.....38
5 1080.....48
6 1084.....8
7 2001.....72
8 2005.....30
9 2017.....106
10 2033.....145
11 2038.....147
12 2051.....160
13 2060.....158

14
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1 P R O C E E D I N G S
2
3 AARON E. MILLER, M.D.,
4 being first duly sworn or affirmed by the Notary,
5 testifies as follows:
6 EXAMINATION
7 BY DR. KAN:
8 Q Good morning. My name is --
9 A Good morning.
10 Q Good morning, Dr. Miller. My name is Cindy
11 Kan, I'm an attorney with the law firm WilmerHale,
12 and with me today is David Bassett, also an attorney
13 at WilmerHale. We represent patent owner Merck
14 Serono, S.A.
15 Dr. Miller, is there any reason that you
16 cannot provide complete and accurate testimony today?
17 A No.
18 Q Do you understand that your testimony here
19 today is given under oath?
20 A Yes.
21 Q You understand that we are taking today's
22 deposition in two IPR proceedings; IPR2023-00480 and

1 IPR2023-00481, correct?
2 A Yes.
3 Q Unless otherwise noted, all exhibits that
4 we use today are being introduced with the same
5 number for both proceedings.
6 I would like to start by handing you what
7 has previously been marked as Exhibit 1084 in
8 IPR2023-480.
9 I'm going to refer to that IPR as "the 480
10 IPR." Okay?
11 A Okay.
12 Q You're familiar with this document,
13 correct?
14 A Yes.
15 Q This is your second declaration providing
16 your opinions regarding U.S. Patent 7,713,947,
17 correct?
18 A That's correct.
19 Q And today I may refer to that patent as the
20 '947 patent, okay?
21 A Okay.
22 Q Could you please turn to page 86 of Exhibit

1084.

A Okay.

Q That is your signature on the declaration, correct?

A It is.

Q You stand by the opinions you provided in your declaration?

A I do.

Q Could you turn to page 10 of Exhibit 1084.

A Okay.

Q At paragraph 20 you state, "In formulating my opinions, I have considered all the references and documents cited herein, including those listed below." Correct?

A Yes.

Q And below is a table that spans pages 10 to 19 of Exhibit 1084, correct?

A Yes.

Q Does this table, in fact, identify all the materials you considered in forming your opinions contained in this declaration?

DR. ELLISON: Objection. Form.

1 A Well, a lot goes into things that I
2 consider, other things that I've read over the years,
3 but these are the documents that I specifically
4 considered in formulating my declaration.
5 Q And you reviewed all the materials listed
6 in this table spanning pages 10 to 19 of Exhibit
7 1084, correct?
8 A Yes, I did.
9 Q Did you talk to anyone, other than counsel
10 for Hopewell, in forming the opinions that are in
11 your second declaration for the 480 IPR?
12 A No.
13 Q I'm going to hand you what has previously
14 been marked as Exhibit 1084 in IPR2023-481. And I
15 may refer to IPR2023-00481 as "the 481 IPR," okay?
16 A Yes.
17 Q You're also familiar with this document,
18 correct?
19 A Yes.
20 Q This is your second declaration providing
21 your opinions regarding U.S. Patent 8,377,903,
22 correct?

1 A Yes.
2 Q And I may refer to you as Patent 8,377,903
3 as "the '903 patent" today, okay?
4 A Okay.
5 Q Could you please turn to the last page of
6 Exhibit 1084, which is page 86.
7 A Yes.
8 Q And that is also your signature shown on
9 the declaration, correct?
10 A Yes.
11 Q You stand by the opinions you provided in
12 your declaration here?
13 A Yes.
14 Q And if you could also turn to page 10 of
15 Exhibit 1084 from the 481 IPR.
16 A Okay.
17 Q At paragraph 20 you state, "In formulating
18 my opinions, I have considered all the references and
19 documents cited herein, including those listed
20 below." Correct?
21 A Yes.
22 Q And below is a table spanning pages 10 to

1 19 of Exhibit 1084, correct?
2 A Yes.
3 Q And again, this table identifies all the
4 materials that you considered in forming your
5 opinions contained in this declaration?
6 DR. ELLISON: Objection. Form.
7 Foundation.
8 A Again, as I said before, I may have
9 considered things that I know from reading other
10 things, but these are the documents I specifically
11 reviewed.
12 Q And as I asked for the 480 IPR, did you
13 talk to anyone, other than counsel for Hopewell, in
14 forming your opinions in the second declaration for
15 the 481 IPR?
16 A No, I did not.
17 Q Did you do anything to prepare for this
18 deposition?
19 A Yes.
20 Q What did you do?
21 DR. ELLISON: I'm going to caution the
22 witness not to divulge the substance of

1 communications with counsel. But you can answer on a
2 high level.
3 A I reviewed my declarations. I reviewed a
4 number of the -- a number of the other documents
5 listed in the materials that I reviewed, and I met
6 with counsel.
7 Q Who did you meet with?
8 A Eldora Ellison and Olga Partington.
9 Q When did you meet them?
10 A I met with them in person over the weekend,
11 Friday and Saturday; that would have been the 10th
12 and 11th of May. I met with them virtually on
13 several occasions. I don't recall off the top of my
14 head the specific dates. It was three or four times.
15 Q And in total, how long would you say you
16 met with them for?
17 A In preparing for this deposition?
18 Q Correct.
19 A Probably somewhere in the vicinity of 15
20 hours.
21 Q In preparing for this deposition, did you
22 communicate with anyone other than counsel for

1 Hopewell?
2 A No.
3 Q In terms of reviewing documents for this
4 deposition, you identified your declarations as well
5 as some of the documents that were cited in that
6 table, correct?
7 A That's correct.
8 Q Did you bring any documents with you today
9 to today's deposition?
10 A In my briefcases are copies of my first and
11 second declarations regarding the '947 patent. I
12 didn't bring anything else with me.
13 Q I see you have some bound copies with you.
14 A These were given to me by counsel this
15 morning.
16 Q And they are?
17 A They are the first and second declarations
18 of both the '947 and the '903 patents.
19 Q Okay. So that would be Exhibit 1002 for
20 the 480 IPR?
21 A Yes.
22 Q And Exhibit 1002 for the 481 IPR, correct?

1 A Yes.
2 Q And there's also two more copies.
3 A My first declaration.
4 Q Okay. So you have both declarations for
5 both proceedings, correct?
6 A Correct.
7 Q Great. Thank you.
8 And none of those documents have any
9 markings in them?
10 A I haven't looked through all the pages of
11 what counsel gave me this morning. But if you would
12 like me to take the time --
13 DR. ELLISON: I can represent there are no
14 markings on them.
15 DR. KAN: Okay. Thank you.
16 Q And you separately did not make any notes
17 or markings in the documents, correct?
18 A That's correct.
19 Q So, Dr. Miller, I know you are familiar
20 with the rules of depositions, but I will add that
21 today, if you need to take a break, just let us know
22 and we'll take a break. I only ask that you wait

1 until after a question has been completed before we
2 do so.
3 A Thank you.
4 Q Okay. Dr. Miller, you consider yourself a
5 practicing clinical expert in multiple sclerosis,
6 correct?
7 A I do.
8 Q In your opinion, a practicing clinical
9 expert in multiple sclerosis would have the knowledge
10 of multiple disciplines, correct?
11 DR. ELLISON: Objection. Form.
12 Foundation.
13 A Yes.
14 Q A practicing clinical expert in multiple
15 sclerosis would have the knowledge of immunology,
16 correct?
17 A Some knowledge of immunology, yes.
18 Q A practicing clinical expert in multiple
19 sclerosis would have knowledge of biochemistry,
20 correct?
21 A Some knowledge of biochemistry.
22 Q A practicing clinical expert in multiple

1 sclerosis would have the knowledge of human
2 physiology and anatomy, correct?
3 A Some knowledge of human physiology and
4 anatomy, correct.
5 Q In your opinion, a practicing clinical
6 expert in multiple sclerosis would be a clinician
7 with experience in neurology, correct?
8 DR. ELLISON: Objection. Form.
9 Foundation.
10 A Could you please repeat that question.
11 Q In your opinion, a practicing clinical
12 expert in multiple sclerosis would be a clinician
13 with experience in neurology, correct?
14 DR. ELLISON: Objection. Form.
15 Foundation.
16 A I don't know what you mean by "experience
17 in neurology." Do you mean they would be a
18 neurologist?
19 Q Well, let's go to Exhibit 1002, your first
20 declaration in the 480 IPR. You can use the ones
21 that counsel gave you, if you prefer.
22 A You wanted my first declaration, right?

1 Q Correct, in the 480 IPR.
2 A Okay.
3 Q If you go to page 14, paragraph 20.
4 A That starts on page 13.
5 Q Yes. So paragraph 20 spans page 13 to 14.
6 But if you go to page 14, where paragraph 20 ends,
7 that last sentence, it states that, "The POSA
8 typically would be a medical doctor with a specialty
9 in neurology, specifically in treating autoimmune
10 disorders of the nervous system, such as multiple
11 sclerosis, and typically at least two years of
12 experience with administering treatments to patients
13 and evaluating results of such treatments, as well as
14 experience or knowledge in related research and
15 development."
16 And actually, in the sentence right before
17 that it says, "Thus, a POSA for the '947 patent would
18 have knowledge" -- "have had the knowledge of
19 multiple disciplines, such as immunology,
20 biochemistry, and human physiology and anatomy, and
21 also typically be a clinician with experience and/or
22 training in neurology."

1 So when you say "experience in neurology,"
2 I'm asking if, in your opinion, a practicing clinical
3 expert in multiple sclerosis would be a clinician
4 with experience in neurology, as you've set forth in
5 paragraph 20 of your declaration?
6 A I don't believe that's the question you
7 asked me originally.
8 Q The question I asked originally was in your
9 experience, a practicing clinical expert in multiple
10 sclerosis would be a clinician with experience in
11 neurology, correct?
12 A You asked me about a clinical expert in
13 multiple sclerosis. This paragraph is referring to a
14 POSA, who is a hypothetical person.
15 Q I understand. And I'm referring to your
16 language of clinician with experience and/or training
17 in neurology because you asked what I was referring
18 to.
19 DR. ELLISON: Objection. Form.
20 Foundation.
21 A But who are you asking about?
22 Q So in the context of your use of

1 "experience and/or training in neurology," I'm asking
2 whether a practicing clinical expert in multiple
3 sclerosis would be a clinician with such experience?
4 A Usually, but not necessarily speaking of
5 neurology as a discipline of training.
6 Q Well, multiple sclerosis is a disease of
7 the central nervous system, correct?
8 A That is correct.
9 Q And neurology is a branch of medicine
10 that's concerned with the study and treatment of
11 disorders of the nervous system, correct?
12 A That is correct.
13 Q So would you expect a practicing clinical
14 expert in multiple sclerosis to be a clinician who
15 has experience in neurology?
16 DR. ELLISON: Objection. Form.
17 Foundation.
18 A Some experience in neurology, but not
19 necessarily formal training as a neurologist.
20 Q In your opinion, a practicing clinical
21 expert in multiple sclerosis would be a medical
22 doctor with a specialty in neurology?

1 A Sometimes.
2 Q In your opinion, a practicing clinical
3 expert in multiple sclerosis would be a medical
4 doctor with experience in treating autoimmune
5 disorders of the nervous system, correct?
6 A Sometimes.
7 Q In your opinion, would a practicing
8 clinical expert in multiple sclerosis be a medical
9 doctor who does not have experience in treating
10 autoimmune disorders of the nervous system?
11 DR. ELLISON: Objection. Form.
12 Foundation. Relevance.
13 A You have to rephrase that question for me,
14 please.
15 Q Well, you said that in response to the
16 question of whether a practicing clinical expert in
17 multiple sclerosis would be a medical doctor with
18 experience in treating autoimmune disorders of the
19 nervous system, your response was "sometimes."
20 So would there be times when a practicing
21 clinical expert would not be a medical doctor who has
22 experience in treating autoimmune disorders?

1 A Yes, sometimes.
2 Q In your opinion, a practicing clinical
3 expert in multiple sclerosis would have experience
4 with administering treatments to multiple sclerosis
5 patients, correct?
6 A Yes.
7 Q In your opinion, a practicing clinical
8 expert in multiple sclerosis would have experience
9 with evaluating results of treatments to multiple
10 sclerosis patients, correct?
11 A Yes.
12 Q In your opinion, a practicing clinical
13 expert in multiple sclerosis would have experience in
14 related research and development?
15 DR. ELLISON: Objection. Form.
16 Foundation.
17 A Please repeat the question.
18 Q In your opinion, a practicing clinical
19 expert in multiple sclerosis would have experience in
20 research and development related to multiple
21 sclerosis?
22 DR. ELLISON: Objection. Form.

1 Foundation.
2 A Often, but not necessarily.
3 Q In your experience, a practicing clinical
4 expert in multiple sclerosis would have knowledge in
5 research and development related to multiple
6 sclerosis?
7 A Yes.
8 Q In your opinion, a practicing clinical
9 expert in multiple sclerosis would know how to
10 research the scientific literature in the field
11 relating to the treatment of autoimmune disorders,
12 correct?
13 A Yes.
14 Q In your opinion, a practicing clinical
15 expert in multiple sclerosis would know how to
16 research the scientific literature in the field
17 relating to various approaches to treating multiple
18 sclerosis, correct?
19 A Yes.
20 Q In your opinion, a practicing clinical
21 expert in multiple sclerosis would have kept himself
22 or herself informed of important clinical trial

1 results of multiple sclerosis drug candidates,
2 correct?
3 A Yes.
4 Q In your opinion, a practicing clinical
5 expert in multiple sclerosis would have knowledge of
6 and skills relating to useful techniques for
7 treatment of multiple sclerosis, correct?
8 DR. ELLISON: Objection. Form.
9 Foundation. Relevance.
10 A Yes.
11 Q I've just handed out Exhibit 1002, which
12 you have your own copy, and we were on paragraph 20,
13 which spans page 13 and 14.
14 Paragraph 20 provides your definition of
15 the person of ordinary skill in the art, correct?
16 A That's correct.
17 Q You still stand by the person of ordinary
18 skill in the art definition, which I will abbreviate
19 as POSA, that you provided in your declaration of
20 Exhibit 1002, correct?
21 A That's correct.
22 Q Based on your definition of a POSA, a POSA

1 for the challenged patents, that is the '947 and '903
2 patents, would not have less than two years of
3 experience with administering treatments to patients
4 and evaluating results of such treatments, correct?
5 DR. ELLISON: Objection. Form.
6 Foundation.
7 A That would be a typical POSA.
8 Q In your opinion, could a POSA for the
9 challenged patents have less than two years of
10 experience with administering treatments to patients
11 and evaluating results of such treatments?
12 A Yes, but not typically.
13 Q A POSA for the challenged patents could
14 have more than two years of experience with
15 administering treatments to patients and evaluating
16 results of such treatments, correct?
17 A That's correct.
18 Q You consider yourself to be a POSA under
19 the definition you provided in paragraph 20 of your
20 first declaration, correct?
21 DR. ELLISON: Objection. Form.
22 Foundation.

1 A No. I consider myself to be an expert in
2 multiple sclerosis.
3 Q In your opinion, do you qualify as a POSA
4 under the definition provided in your first
5 declaration, Exhibit 1002, at paragraph 20?
6 DR. ELLISON: Objection. Form.
7 Foundation.
8 A No, I'm not a hypothetical person.
9 Q At a minimum, do you qualify as a POSA
10 under the definition provided in your definition?
11 DR. ELLISON: Objection. Form.
12 Foundation.
13 A A POSA is a hypothetical person who is
14 aware of all pertinent art. I believe that's a legal
15 concept. I don't believe that any actual practicing
16 expert in anything is aware of all pertinent art.
17 Q Based on your definition of a POSA, a POSA
18 for the challenged patents would have had the
19 knowledge of multiple disciplines, such as
20 immunology, biochemistry, and human physiology and
21 anatomy, correct?
22 A Yes, that's correct.

1 Q A POSA for the challenged patents could
2 have knowledge from other disciplines, in addition to
3 immunology, biochemistry, and human physiology and
4 anatomy, correct?
5 A Yes, he or she could.
6 Q Would a person who lacks knowledge of
7 immunology be excluded from your definition of a POSA
8 for the challenged patents?
9 A The POSA, as described in my declaration,
10 would be expected to have had some knowledge of
11 immunology.
12 Q And if that person, as described in your
13 declaration, lacks knowledge of immunology, would
14 that person be excluded from your definition of a
15 POSA?
16 A A POSA lacking any knowledge of immunology
17 would not have been included in my definition of a
18 POSA.
19 Q And a POSA lacking any knowledge of
20 biochemistry, would they be excluded from your
21 definition of a POSA?
22 A A person lacking any knowledge of

1 biochemistry would not have been included in my
2 definition of a POSA.
3 Q And a person lacking any knowledge of human
4 physiology and anatomy would also be excluded from
5 your definition of a POSA?
6 A Yes.
7 Q Based on your definition of a POSA, a
8 person who meets all of your criteria and has
9 additional medical or clinical experience would still
10 qualify as a POSA for the challenged patents,
11 correct?
12 A Yes.
13 Q Based on your definition of a POSA, a
14 person who -- strike that.
15 Based on your definition of a POSA, a
16 person would need to meet all of your criteria to --
17 to qualify as a POSA for the challenged patents,
18 correct?
19 DR. ELLISON: Objection. Form.
20 Foundation.
21 A A typical POSA would have had all those
22 qualities.

1 Q Doctor, in your opinion, is a reduction in
2 inflammation in a multiple sclerosis patient using a
3 multiple sclerosis drug a measure of that drug's
4 therapeutic efficacy?
5 DR. ELLISON: Objection. Form.
6 Foundation.
7 A Could you please repeat the question.
8 Q In your opinion, is a reduction in
9 inflammation in a multiple sclerosis patient using a
10 multiple sclerosis drug a measure of that drug's
11 therapeutic efficacy?
12 DR. ELLISON: Objection. Form.
13 Foundation.
14 A We don't typically measure inflammation in
15 people with MS.
16 Q Would a reduction in inflammation in an MS
17 patient using an MS drug indicate that drug's
18 efficacy?
19 DR. ELLISON: Objection. Form.
20 Foundation.
21 A I -- if we were to measure inflammation, it
22 would be one potential measure of efficacy.

1 Q And when you say "we don't typically
2 measure inflammation in people with MS," have you
3 ever, in your experience, measured inflammation in
4 people with MS?
5 A No.
6 Q Corticosteroids reduce inflammation in
7 multiple sclerosis patients, correct?
8 A They're thought to do so.
9 Q But corticosteroids do not have any
10 long-term benefits for multiple sclerosis patients,
11 correct?
12 DR. ELLISON: Objection. Form.
13 Foundation.
14 A You would have to define your terms better.
15 Q I'm going to hand you what has previously
16 been marked as Exhibit 2005 in both the 480 and 481
17 IPRs. You recognize Exhibit 2005?
18 A I do.
19 Q And if you turn to page 48 of Exhibit
20 2005 -- sorry.
21 Exhibit 2005 is a book chapter that is
22 titled -- okay, the book is titled, "Multiple

1 Sclerosis: The Questions You Have - The Answers You
2 Need" by Rosalind Kalb. And specifically we have an
3 excerpt of chapter 3, which you co-authored, correct?
4 A Yes.
5 Q And this book chapter is, I believe, from
6 2000.
7 So going back to page 48 of Exhibit 2005,
8 the first sentence on the top of page 48 states,
9 "Continuous administration of steroids has never been
10 shown to provide long-term benefits for people with
11 MS." Correct?
12 A Yes, that's what this sentence says.
13 Q So I will re-ask the question from before,
14 which is that corticosteroids -- at least continuous
15 administration of corticosteroids has never been
16 shown to provide long-term benefits for people with
17 MS, correct?
18 DR. ELLISON: Objection. Form.
19 Foundation.
20 A Yes, in the sense that I was understanding
21 long-term benefits.
22 Q And how would you understand the term

1 "long-term benefits"?
2 A For many months or years.
3 Q So the reduction in inflammation caused by
4 corticosteroids would not be a measure of a
5 therapeutic efficacy of corticosteroids, correct?
6 A We don't generally measure inflammation.
7 Q But would the reduction in inflammation
8 caused by corticosteroids be a measure of the
9 therapeutic efficacy of corticosteroids?
10 A We don't measure inflammation.
11 Q If you were to measure inflammation, would
12 the reduction of inflammation caused by
13 corticosteroids be a measure of the therapeutic
14 efficacy of corticosteroids?
15 A If we were to measure inflammation, a
16 reduction in inflammation would probably be a
17 property of corticosteroids.
18 Q In your opinion, would a reduction in
19 inflammation in a multiple sclerosis patient using a
20 disease-modifying drug be a measure of that drug's
21 therapeutic efficacy?
22 A We don't measure inflammation.

1 Q And again, if you were to measure
2 inflammation in a multiple sclerosis patient who was
3 using a disease-modifying drug, would that reduction
4 in inflammation be a measure of that drug's
5 therapeutic efficacy?
6 A A reduction of inflammation where?
7 Q Well, let me ask a more specific question.
8 In your opinion, is a reduction in
9 inflammation in a multiple sclerosis patient using
10 cladribine a goal of cladribine's treatment?
11 A We don't measure reduction of inflammation
12 in patients with MS receiving cladribine.
13 Q Is there any way to measure a reduction in
14 inflammation in a multiple sclerosis patient
15 receiving cladribine?
16 DR. ELLISON: Objection. Form.
17 Foundation. Relevance.
18 A We don't directly measure inflammation or
19 reduction of inflammation.
20 Q So in your opinion, would it be possible to
21 indirectly measure a reduction in inflammation in a
22 multiple sclerosis patient using cladribine?

1 A I don't know what you mean by "indirectly
2 measure."
3 Q Well, you say you do not directly measure.
4 A We may -- we may infer a reduction in
5 inflammation.
6 Q And how would you infer a reduction in
7 inflammation in a multiple sclerosis patient using
8 cladribine?
9 A We could measure a reduction in
10 inflammation -- or we could infer a reduction in
11 inflammation by seeing a reduction in new gadolinium
12 -- g-a-d-o-l-i-n-i-u-m -- a reduction in new
13 gadolinium-enhanced lesions. We could infer a
14 reduction in inflammation by a decrease in the number
15 of relapses a patient with multiple sclerosis was
16 having. We could infer a reduction in inflammation
17 by a reduction in the number of T2 lesions we saw
18 compared to a prior scan, prior MRI scans.
19 Q Would a reduction in T2 lesions necessarily
20 indicate a reduction in inflammation?
21 A Generally, that would be the case.
22 Q And would a decrease in the number of

1 relapses in a patient indicate a reduction in
2 inflammation necessarily?
3 DR. ELLISON: Objection. Form.
4 A I would infer that a reduction in relapses
5 would imply a reduction in inflammation.
6 Q But not necessarily?
7 DR. ELLISON: Objection. Form.
8 A Generally, that would be the case.
9 Q And would observing a reduction in new
10 gadolinium-enhanced lesions necessarily indicate a
11 reduction in inflammation?
12 A Generally, that would be the case.
13 Q In your opinion, could you infer a
14 reduction in inflammation by measuring a change in
15 lymphocyte counts due to lymphocyte suppression?
16 A Please repeat the question.
17 Q I'll do my best.
18 I think I said in your opinion, could you
19 infer a reduction in inflammation by measuring a
20 change in lymphocyte counts due to lymphocyte
21 suppression?
22 A No.

1 Q In your opinion, in the context of multiple
2 sclerosis, the goal of lymphocyte suppression is to
3 reach a lymphocyte nadir, correct?
4 A I wouldn't put it that way.
5 Q Okay. In your opinion, in the context of
6 multiple sclerosis, what would be the goal of
7 lymphocyte suppression?
8 A The goal of lymphocyte suppression in
9 multiple sclerosis would be to try to bring about a
10 reduction in inflammation; meaning, clinically, a
11 result resulting in diminished relapses.
12 Q Would reaching a lymphocyte nadir -- strike
13 that.
14 In your opinion, if you gave a patient, a
15 multiple sclerosis patient, a drug that causes
16 lymphocyte suppression, would reaching a lymphocyte
17 nadir with that drug tell you anything with respect
18 to treating MS?
19 DR. ELLISON: Objection. Form.
20 Foundation.
21 A I find that question too broad and I can't
22 answer it the way you phrased it.

1 Q If a patient administered with cladribine
2 results in lymphocyte suppression such that the
3 lymphocytes reach a lymphocyte nadir, what would that
4 tell you with respect to the effect of cladribine in
5 treating that patient?
6 DR. ELLISON: Objection. Form.
7 Foundation.
8 A It would only have told me that the
9 administration of cladribine reduced the lymphocyte
10 count.
11 Q If cladribine causes a reduction in
12 lymphocyte count such that the lymphocytes reach a
13 nadir, does that mean that cladribine has therapeutic
14 efficacy against multiple sclerosis?
15 DR. ELLISON: Objection. Form.
16 Foundation.
17 A First of all, I don't know what you mean by
18 "a nadir." I mean, I know the definition of nadir,
19 but I don't know what you mean.
20 Q But you've heard of the term "lymphocyte
21 nadir," correct?
22 A I probably have heard that term.

1 Q And you've used the term yourself in
2 describing lymphocyte suppression levels, correct?
3 A I might have. I can't remember
4 specifically.
5 Q Let me introduce what was previously --
6 what has previously been marked as Exhibit 1013 in
7 both IPR proceedings.
8 A Okay. This calls for glasses.
9 Q Exhibit 1013 is a reference by Stelmasiak
10 -- S-t-e-l-m-a-s-i-a-k -- titled, "A Pilot Trial of
11 Cladribine, (2 chlorodeoxyadenosine)" --
12 c-h-l-o-r-o-d-e-o-x-y-a-d-e-n-o-s-i-n-e -- "in
13 Remitting-Relapsing Multiple Sclerosis," correct?
14 A Yes.
15 Q And if you turn to page 5 of Exhibit 1013,
16 and I'm referring to the native page numbering.
17 A Okay.
18 Q There's a Figure 1 on the right-hand column
19 at the bottom showing average lymphocyte counts
20 during and after treatment with cladribine, correct?
21 A Yes.
22 Q And above that -- above that Figure 1, it

1 states five lines from the -- from Figure 1, it
2 states, [As read:] "Lymphocyte counts dropped from
3 the initial count of 2,336 plus or minus 595 per
4 microliters (mean plus or minus standard deviation)
5 to 968 plus or minus 229 per microliters at six
6 months and remained at approximately 1,000 per
7 microliter for the next 15 months, correct?
8 A Yes.
9 Q Would you agree that the decrease from
10 lymphocyte counts to 968 plus or minus 229 at six
11 months is a lymphocyte nadir?
12 A It was a mean lymphocyte nadir.
13 Q And if cladribine causes lymphocytes to
14 reach a nadir, would that indicate cladribine's
15 therapeutic efficacy?
16 DR. ELLISON: Objection. Form.
17 Foundation.
18 A It could indicate that cladribine had
19 reduced the lymphocyte counts significantly.
20 Q So if a certain dose of cladribine causes a
21 patient's lymphocyte levels to reach a nadir, does
22 that mean the patient should not receive additional

1 doses of cladribine?
2 DR. ELLISON: Objection. Form.
3 Foundation.
4 A Not necessarily.
5 Q So in your opinion, if a certain dose of
6 cladribine causes a patient's lymphocyte levels to
7 reach a nadir, the patient could still receive
8 additional doses of cladribine, correct?
9 A Possibly.
10 Q In your opinion, does the magnitude of
11 lymphocyte suppression correlate with changes in
12 EDSS?
13 DR. ELLISON: Objection. Form.
14 Foundation.
15 A Not necessarily.
16 Q In your opinion, does the magnitude of
17 lymphocyte suppression correlate with changes in
18 relapse rate?
19 A Not necessarily.
20 Q In your opinion, does the magnitude of
21 lymphocyte suppression correlate with changes in
22 disease progression?

1 DR. ELLISON: Objection. Form.
2 Foundation.
3 A Not necessarily.
4 Q In your opinion, does the magnitude of
5 lymphocyte suppression correlate with any multiple
6 sclerosis outcome measure?
7 DR. ELLISON: Objection. Form.
8 Foundation.
9 A Too broad a question. There's too many
10 potential outcome measures which have not been
11 examined with relationship to lymphocyte counts.
12 Q Does the magnitude of lymphocyte
13 suppression correlate with MRI outcome measures?
14 DR. ELLISON: Objection. Form.
15 Foundation.
16 A Not necessarily.
17 Q In your opinion, lymphocytes do not need to
18 be suppressed to below 1,000 cells per microliter to
19 achieve a therapeutic effect, correct?
20 A As asked, that's correct; they do not need
21 to be suppressed.
22 Q Sorry, just to clarify, they do not need to

1 be suppressed to below 1,000 cells per microliter,
2 correct?
3 A They don't necessarily need to be
4 suppressed at all to treat multiple sclerosis.
5 Q And as you understood the question I just
6 asked before, which is -- which was, in your opinion,
7 lymphocytes do not need to be suppressed to below
8 1,000 cells per microliter to achieve a therapeutic
9 effect, in your opinion, does a therapeutic effect
10 mean the same thing as therapeutic efficacy?
11 DR. ELLISON: Objection. Form.
12 Foundation.
13 A A therapeutic effect does not, in my
14 opinion, mean the same thing as efficacy.
15 Q In your opinion, lymphocytes do not need to
16 be suppressed to below 1,000 cells per microliter to
17 achieve a treatment response, correct?
18 DR. ELLISON: Objection. Form.
19 Foundation.
20 A In order to achieve a treatment response in
21 multiple sclerosis, one doesn't necessarily need to
22 lower the lymphocyte count.

1 Q So in your opinion, a treatment response in
2 multiple sclerosis could occur without any
3 suppression of lymphocyte counts, correct?
4 A A treatment response to multiple sclerosis
5 doesn't necessarily entail a reduction in lymphocyte
6 count.
7 Q And with respect to the term "a treatment
8 response," does that mean the same thing as
9 therapeutic efficacy?
10 A Not in my opinion.
11 Q In your opinion, would the threshold of
12 reducing lymphocyte counts to 1,000 cells per
13 microliter be an example of a lymphocyte level that
14 constitutes immune suppression?
15 DR. ELLISON: Objection. Form.
16 Foundation.
17 A Please repeat the question.
18 Q In your opinion, 1,000 cells per microliter
19 is an example of a lymphocyte level that constitutes
20 immune suppression, correct?
21 DR. ELLISON: Objection. Form.
22 Foundation.

1 A Usually, but not always.
2 Q In your opinion, are there any other
3 lymphocyte levels that would constitute immune
4 suppression?
5 DR. ELLISON: Objection. Form.
6 Foundation.
7 A It's not a specific level. It depends
8 where you started from.
9 Q Is there a relative reduction in lymphocyte
10 levels that would constitute immune suppression, in
11 your opinion?
12 DR. ELLISON: Objection. Form.
13 Foundation.
14 A I don't have a specific value in mind.
15 Q Would any reduction in lymphocyte levels
16 constitute immune suppression?
17 A Well, suppression, to me, means a reduction
18 from a former state.
19 Q So would any reduction in lymphocyte level
20 from a former state constitute suppression?
21 A I wouldn't consider that necessarily to be
22 the case.

1 Q But you also don't have a specific value in
2 mind in terms of a relative reduction in lymphocyte
3 suppression that would constitute immune suppression,
4 correct?
5 A I don't have a specific percentage in mind.
6 Q Would a 50 percent reduction in lymphocyte
7 levels constitute immune suppression?
8 A Sometimes.
9 Q But sometimes not?
10 A Sometimes not.
11 Q Would a 25 percent reduction in lymphocyte
12 count constitute lymphocyte suppression?
13 A In using the term "suppression" as a
14 reduction from a former state, any percent could be
15 considered suppression.
16 DR. KAN: Okay. We've been going for about
17 an hour. Would you like to take a break?
18 THE WITNESS: Sure.
19 (Recess 10:01 a.m. - 10:12 a.m.)
20 BY DR. KAN:
21 Q Dr. Miller, in your opinion, a POSA would
22 have understood Bodor's bioavailability to be at

1 least comparable to Stelmasiak's, correct?
2 A Yes.
3 Q In your opinion, Stelmasiak's solution has
4 a bioavailability of 37 percent to 51 percent,
5 correct?
6 A I don't believe that Stelmasiak measured
7 the bioavailability of his solution.
8 Q If you go to your second declaration,
9 Exhibit 1084, and we'll refer to the one in the 480
10 IPR. Let's see, at paragraph 60, the bottom of page
11 41 to the top of page 42, in the first sentence of
12 paragraph 60, you state, "Drs. Lublin and Meibohm" --
13 A Wait. Hold on. I don't think I'm with
14 you.
15 Q Exhibit 1084, 480 IPR.
16 A Oh, sorry.
17 Q That's okay.
18 A What was the page again?
19 Q 41 to 42, paragraph 60.
20 A Page 41?
21 Q Yes. Are you there?
22 A Yes.

1 Q Okay. The first sentence in paragraph 60
2 of Exhibit 1084, you stated, "Drs. Lublin and
3 Meibohm" -- M-e-i-b-o-h-m -- "also mischaracterize
4 the bioavailability of Stelmasiak's cladribine
5 solution by ignoring the art that discloses a range
6 of bioavailabilities (37 percent to 51 percent) for
7 oral cladribine solutions, such as that used in
8 Stelmasiak." Correct?
9 A Yes.
10 Q So here you're suggesting that oral
11 cladribine solutions, such as the one used in
12 Stelmasiak, has a range of bioavailability from 37
13 percent to 51 percent, correct?
14 A Yes.
15 Q So in your opinion, Bodor's oral tablets
16 have a bioavailability of 35.7 percent to 52.1
17 percent, correct?
18 A Yes.
19 Q In preparing your opinions for your second
20 declaration in these proceedings, that is, Exhibit
21 1084, you have reviewed the declaration that
22 Dr. Pinal, P-i-n-a-l, provided in each of these

1 proceedings, correct?
2 A I have reviewed those, yes.
3 Q Do you rely on Dr. Pinal for opinions on
4 Bodor's bioavailability?
5 DR. ELLISON: Objection. Form.
6 Foundation.
7 A In formulating my declarations, I didn't
8 need to rely on Dr. Pinal's declarations, but I was
9 glad that it supported my views.
10 Q So you did not need to rely on Dr. Pinal's
11 opinions from his declarations. But do you agree
12 with all of his opinions from his declaration, as set
13 forth in Exhibit 1080?
14 A I can't recall off the top of my head what
15 all the statements in Pinal's declaration were, so I
16 can't answer that question.
17 Q Do you recall -- during your review of
18 Dr. Pinal's declaration, do you recall disagreeing
19 with any of his opinions?
20 A I don't have any specific recollections
21 about that. I didn't rely on Dr. Pinal's declaration
22 in formulating my own declarations.

1 Q Okay. Do you agree that the difference
2 between the bioavailability range for Bodor's
3 formulation, which we just identified as 35.7 percent
4 to 52.1 percent, and the bioavailability range for
5 Stelmasiak's formulation, which we identified as 37
6 percent to 50 percent -- 51 percent, sorry -- is
7 insignificant?
8 DR. ELLISON: Objection. Form.
9 Foundation.
10 A I believe these are -- these are
11 overlapping ranges which may be -- may be the same,
12 may imply that Bodor's formulation is -- has greater
13 bioavailability. By these numbers, Bodor's
14 bioavailability is at least comparable to
15 Stelmasiak's, if not higher.
16 Q Could Bodor's bioavailability be lower than
17 Stelmasiak's, based on those ranges?
18 A Bodor's bioavailability overlaps that of
19 Stelmasiak's and could easily be higher. And there
20 are other important characteristics of Bodor's
21 formulation, and he -- he states in his patent that
22 it has a greater bioavailability, improved

1 bioavailability, and a POSA would have no reason to
2 doubt that.
3 Q But based on the ranges that we just
4 identified for each of Bodor's formulation and
5 Stelmasiak's formulation, could Bodor's
6 bioavailability be lower than Stelmasiak's?
7 A Well, Stelmasiak didn't measure his own
8 bioavailability, so I don't know.
9 Q But you agree that Stelmasiak's formulation
10 is an example of the oral cladribine formulations
11 that were known which had bioavailabilities of 37
12 percent to 51 percent, correct?
13 A Stelmasiak's formulation was comparable to
14 what was measured by Liliemark and that's the range
15 that Liliemark obtained.
16 Q And in your opinion, the difference between
17 that range and Bodor's range, do you consider that
18 difference insignificant?
19 A Bodor's range was at least comparable to,
20 if not greater than the range that Liliemark found.
21 Q I'm going to hand you what has previously
22 been marked as Exhibit 1080 in the 480 IPR. This is

1 the declaration of Rodolfo, R-o-d-o-l-f-o, Pinal,
2 P-i-n-a-l. Correct?
3 A Yes.
4 Q And you've reviewed this declaration,
5 correct?
6 A Yes.
7 Q If you would please turn to page 40 of
8 Exhibit 1080, paragraph 76, and take a minute to read
9 that paragraph. And let me know when you're done.
10 Dr. Miller?
11 A I've finished reading. Sorry.
12 Q The last sentence in paragraph 76,
13 Dr. Pinal states, "The difference between Bodor's
14 35.7 to 52.1 percent range and the prior art (and
15 thus Stelmasiak's) 37 to 55 percent range is
16 insignificant." Do you see that?
17 A I see it.
18 Q Do you agree with Dr. Pinal's opinion as
19 stated in that last sentence of paragraph 76?
20 A Although I agree that the difference in
21 those ranges is not significant, Bodor's formulation
22 may well have been of higher -- of higher

1 bioavailability than Stelmasiak's.
2 Q Would you agree that for cladribine
3 formulations, a formulation having a higher
4 bioavailability is preferable to a formulation having
5 a lower bioavailability?
6 DR. ELLISON: Objection. Form.
7 Foundation.
8 A Please repeat the question.
9 Q Would you agree that for a cladribine
10 formulation, a formulation having a higher
11 bioavailability is preferable to a formulation having
12 a lower bioavailability?
13 A There are many characteristics that might
14 make -- that one might -- that might make one oral
15 formulation better than another. Higher
16 bioavailability would be only one of a number of
17 features potentially. So it's not necessarily the
18 case that that would be a better preparation.
19 Q And if all these other characteristics are
20 equal, with the exception of bioavailability, would a
21 formulation having a higher bioavailability be
22 preferable to a formulation having a lower

1 bioavailability?
2 DR. ELLISON: Objection. Form.
3 Foundation.
4 A Well, a POSA would have understood that
5 Bodor's oral preparation had other qualities that
6 made it superior to Stelmasiak's, irrespective of the
7 exact bioavailability.
8 Q And assuming that these other aspects of
9 Bodor's formulation were the same, would a cladribine
10 formulation having a higher bioavailability be
11 preferable to a cladribine formulation having a lower
12 bioavailability?
13 DR. ELLISON: Objection. Form.
14 Foundation.
15 A Please repeat the question.
16 Q Assuming that these other aspects of
17 Bodor's formulation were the same for Stelmasiak's
18 formulation, would a cladribine formulation having a
19 higher bioavailability be preferable to a cladribine
20 formulation having a lower bioavailability?
21 DR. ELLISON: Objection. Form.
22 Foundation.

1 A But Bodor's formulation doesn't have the
2 same other -- other characteristics as Stelmasiak's
3 preparation. So a POSA would have no reason to doubt
4 Bodor's conclusion that his preparation had better --
5 had better availability or had better properties than
6 the Stelmasiak solution.
7 Q I understand that your opinion is that
8 Bodor's formulation doesn't have the same other
9 characteristics.
10 What I'm asking is if everything else being
11 equal, that is, all characteristics other than
12 bioavailability were the same, would a formulation
13 having a higher bioavailability be preferable to a
14 formulation having a lower bioavailability?
15 DR. ELLISON: Objection. Form.
16 Foundation.
17 A Although that would be true, I have no
18 reason to doubt that Bodor's formulation would not
19 have had at least comparable, if not higher
20 bioavailability, than Stelmasiak's.
21 Q Would a cladribine formulation having a
22 bioavailability of 55 percent be preferable --

1 A How much? I'm sorry.
2 Q -- 55 percent, be preferable to a
3 cladribine formulation having a bioavailability of 52
4 percent, all else being equal?
5 DR. ELLISON: Objection. Form.
6 Foundation.
7 A Well, 55 is a higher number than 52.
8 Q As such, would a cladribine formulation
9 having a bioavailability of 55 percent be preferable
10 to a cladribine formulation having a bioavailability
11 of 52 percent, all else being equal?
12 DR. ELLISON: Objection. Form.
13 Foundation. Relevance.
14 A When you measure bioavailability, you never
15 get an absolute number. There's too much variation
16 from test to test, from patient to patient, even
17 within the same patient. So it's never going to be
18 that it comes out to absolutely 55 percent versus 52
19 percent.
20 So I can't really say that measuring it at
21 55 percent would necessarily be better than 52
22 percent, because those I do not think are realistic

1 numbers.
2 Q Do you think the difference between the
3 value of 55 percent and 52 percent would be
4 insignificant?
5 DR. ELLISON: Objection. Form.
6 Foundation. Relevance.
7 A Insignificant in regard to what?
8 Q The difference of those values with respect
9 to bioavailability.
10 DR. ELLISON: Objection. Form.
11 Foundation. Relevance.
12 A Significance in -- significant in what
13 respect?
14 Q In the respect of bioavailabilities of
15 those two formulations.
16 DR. ELLISON: Objection. Form.
17 Foundation. Relevance.
18 A I'm not a pharmacologist, but I would doubt
19 that a difference between 55 percent and 52 percent
20 would be of much -- of much significance, especially
21 of much clinical significance.
22 Q Do you agree that the bioavailability of

1 Bodor's dose is about 40 percent?
2 A As Bodor stated, the bioavailability, I
3 think, was between 37.9 and 52.1 percent.
4 Q You --
5 A 35.7 and 50.1, I'm sorry.
6 Q You still have Dr. Pinal's declaration,
7 Exhibit 1080, in front of you?
8 A Yes, I do.
9 Q Could you go to pages 42 to 43.
10 A All right.
11 Q Paragraph 81, which spans both those pages,
12 Dr. Pinal states in paragraph 81, "A POSA, as advised
13 by a pharmacologist, would have understood that
14 Bodor's oral dose, corrected for its bioavailability
15 (about 40 percent) is the dose (in milligrams per
16 kilogram) times 0.4 (i.e., 40 percent
17 bioavailability)."
18 Do you see that sentence?
19 A Yes, I do.
20 Q Dr. Pinal is opining that Bodor's oral dose
21 has a bioavailability of about 40 percent, correct?
22 DR. ELLISON: Objection. Form.

1 Foundation.
2 A That's the opinion he states.
3 Q Do you agree with Dr. Pinal's opinion at
4 paragraph 81 regarding the bioavailability of Bodor's
5 oral dose?
6 A As Bodor stated, the bioavailability was
7 35.7 to 52.1 percent.
8 Q So you disagree with Dr. Pinal's opinion as
9 set forth at paragraph 81?
10 DR. ELLISON: Objection. Form.
11 Foundation.
12 A I don't disagree with his opinion. That's
13 his opinion and I only know that numbers that were
14 stated in Bodor's experimentation.
15 Q If you don't disagree with Dr. Pinal's
16 opinion at paragraph 81, do you agree with
17 Dr. Pinal's opinion at paragraph 81?
18 DR. ELLISON: Objection. Form.
19 A I don't have an opinion about that.
20 Q In your opinion, is Dr. Pinal incorrect
21 with respect to his opinion at paragraph 81 regarding
22 Bodor's bioavailability?

1 A I don't have an opinion that he's incorrect
2 because that 40 percent is within the range, but I
3 stand by the fact that Bodor's range of
4 bioavailability was 35.7 percent to 52.1 percent.
5 Q So you're unable to agree with Dr. Pinal's
6 opinion, as set forth --
7 DR. ELLISON: Objection --
8 Q -- in paragraph 81?
9 DR. ELLISON: Objection. Form.
10 Foundation.
11 A I don't have an opinion about that.
12 Q In your opinion, given the comparable
13 bioavailability between Bodor's formulation and
14 Stelmasiak's formulation, Bodor's maximum dose of 140
15 milligrams cladribine is close to Stelmasiak's 150
16 milligram dose, correct?
17 DR. ELLISON: Objection. Foundation.
18 Form.
19 A Please repeat the question.
20 Q In your opinion, given the comparable
21 bioavailability between Bodor's formulation and
22 Stelmasiak's formulation, Bodor's maximum dose of 140

1 milligrams of cladribine is close to Stelmasiak's 150
2 milligram dose, correct?
3 DR. ELLISON: Objection. Foundation.
4 Form.
5 A I believe that it's likely that Bodor's
6 dose was at least comparable to, if not higher, in
7 bioavailability to Stelmasiak's. And I believe that
8 there are other features, as cited by Bodor, that
9 made it a preferable formulation than Stelmasiak's.
10 And I have no reason to doubt a POSA would
11 have no reason to doubt that Bodor's conclusion that
12 -- that his bioavailability was better, was improved.
13 Q Could you go to your declaration, Exhibit
14 1084 in the 480 IPR, to paragraph 94 which spans
15 pages 65 to 66.
16 A This is the second declaration you're
17 referring to?
18 Q Correct, this is your second declaration.
19 A And what were the page numbers?
20 Q 65 to 66.
21 A Okay.
22 Q So at paragraph 94, the last sentence

1 starts at the bottom of page 65, and you state, [As
2 read]: "Because Bodor's bioavailability is at least
3 comparable to Stelmasiak's, and Bodor's maximum dose
4 is close to Stelmasiak's dose, as Lublin agrees
5 (Exhibit 2051 paragraph 172) a POSA would have
6 expected Bodor's dosing regimen to reduce or maintain
7 patients' EDSS scores, which is a metric of efficacy
8 in light of Stelmasiak." Correct?
9 A Yes.
10 Q So in your opinion, given the comparable
11 bioavailability, Bodor's maximum dose of 140
12 milligrams cladribine is close to Stelmasiak's 150
13 milligram oral dose, correct?
14 A As Dr. Lublin agreed.
15 Q And that is your opinion, correct?
16 A That is my opinion, yes.
17 Q So in your opinion, is Bodor's -- strike
18 that.
19 In your opinion, Bodor's maximum dose of
20 140 milligrams of oral cladribine would be similar to
21 Stelmasiak's 150 milligram oral dose of cladribine,
22 correct?

1 DR. ELLISON: Objection. Form.
2 Foundation.
3 A Bodor's maximum dose would be close to
4 Stelmasiak's dose.
5 Q And Bodor's maximum dose would also be
6 similar to Stelmasiak's dose, correct?
7 DR. ELLISON: Objection. Form.
8 Foundation.
9 A Well, I would interpret "close to" as being
10 similar to. But as Bodor stated, it would still have
11 features that made it a preferable preparation and
12 probably higher bioavailability.
13 Q So if Bodor's maximum 140 milligram dose is
14 similar to Stelmasiak's dose of 150 milligrams oral
15 cladribine, a POSA would have expected Bodor's dose
16 to have similar effects as Stelmasiak's dose,
17 correct?
18 DR. ELLISON: Objection. Form.
19 Foundation.
20 A I don't believe that that was Stelmasiak's
21 oral dose.
22 Q We're referring to Stelmasiak 's oral dose

1 after three months.
2 A You didn't state that. So Bodor's maximum
3 dose was close to that dose of Stelmasiak.
4 Q Okay. So, sorry, just for context, if we
5 go back to paragraph 94, where this discussion
6 started, about four lines in, we referred to
7 Stelmasiak's lower dose of 150 milligram. And I
8 believe we are referring to Stelmasiak's oral dose of
9 150 milligrams.
10 A Okay.
11 Q So let me repeat the question.
12 If Bodor's maximum 140 milligram dose is
13 similar to Stelmasiak's dose of 150 milligrams of
14 oral cladribine, a POSA would have expected Bodor's
15 dose to have similar effects as Stelmasiak's dose,
16 correct?
17 DR. ELLISON: Objection. Form.
18 Foundation.
19 A A POSA would have expected Bodor's dose to
20 have -- to do at least as well and likely better than
21 that of Stelmasiak.
22 Q So in your opinion, a POSA would have

1 expected Bodor's dose to have at least similar
2 effects as Stelmasiak's, correct?
3 A I think that Bodor's preparation would have
4 been expected to have -- likely have better effects
5 than Stelmasiak's.
6 Q So better but not similar than
7 Stelmasiak's, in your opinion?
8 A At least as good, if not better.
9 Q In your opinion, a POSA would have expected
10 Bodor's maximum dose of 140 milligrams oral
11 cladribine to have similar lymphocyte effects as
12 Stelmasiak's 150 milligrams oral cladribine dose,
13 correct?
14 DR. ELLISON: Objection. Form.
15 Foundation.
16 A Please reread the question, please.
17 Q In your opinion, a POSA would have expected
18 Bodor's maximum dose of 140 milligrams oral
19 cladribine to have similar lymphocyte effects as
20 Stelmasiak's 150 milligrams oral cladribine dose,
21 correct?
22 DR. ELLISON: Objection. Form.

1 Foundation.
2 A I wouldn't be able to know that.
3 Q If we go -- if we go back to paragraph 94
4 of your Exhibit 1084, the last sentence in paragraph
5 84, at the top of page 66, where you state, Because
6 the bioavailability of Bodor's solution is at least
7 comparable to Stelmasiak's, the last part of the
8 opinion you state, "a POSA would have expected
9 Bodor's dosing regimen to reduce or maintain
10 patients' EDSS scores, which is a metric of efficacy
11 in light of Stelmasiak." Correct?
12 A Yes.
13 Q So in your opinion, you would know whether
14 a POSA would have expected Bodor's dosing regimen to
15 reduce or maintain patients' EDSS scores in light of
16 Stelmasiak, but you can't comment as to whether a
17 POSA would have expected Bodor's dosing regimen to
18 reduce or have the same effect on lymphocytes.
19 A You didn't ask me about Bodor's dosing
20 regimen.
21 Q My previous question was, in your opinion,
22 a POSA would have expected Bodor's maximum dose of

1 140 milligrams oral cladribine to have similar
2 lymphocyte effects as Stelmasiak's 150 milligrams
3 oral cladribine dose, correct?
4 A I may have misunderstood your question.
5 So I would have expected Bodor's maximum
6 dose potentially to have that same effect on
7 lymphocytes.
8 Q Dr. Miller, as a practicing clinical
9 expert, you have treated thousands of MS patients
10 since the beginning of your career in 1977, correct?
11 A That's correct.
12 Q In the course of treating these thousands
13 of MS patients, you have prescribed medications for
14 these patients, correct?
15 A Correct.
16 Q What medications have you prescribed for
17 your MS patients?
18 A Can you be a little bit more specific in
19 that question?
20 Q Have you prescribed dose-modifying
21 therapies for your MS patients?
22 DR. ELLISON: Objection. Form.

1 A What do you mean by dose-modifying
2 medications?
3 Q Apologies. Disease-modifying therapies.
4 A Yes.
5 Q What disease-modifying therapies have you
6 prescribed for your MS patients?
7 A I've prescribed a number of different
8 preparations of interferons. I've prescribed
9 copaxone, and later generics known as glatiramer
10 acetate. I've prescribed natalizumab. I've
11 prescribed fingolimod. I've prescribed dimethyl
12 fumarate. I've prescribed diroximel fumarate;
13 d-i-r-o-x-i-m-e-l, f-u-m-a-r-a-t-e. I've prescribed
14 Zeposia. I've prescribed Tascenso ODT;
15 T-a-s-c-e-n-s-o, dash O-D-T. I've prescribed
16 Ocrevus, O-c-r-e-v-u-s. I've prescribed Kesimpta,
17 K-e-s-i-m-p-t-a. I've prescribed Briumvi,
18 B-r-i-u-m-v-i. I've prescribed cladribine, known as
19 Mavenclad. I've prescribed mitoxantrone,
20 m-i-t-o-x-a-n-t-r-o-n-e. I've prescribed rituximab.
21 I may have forgotten one or two, but I've
22 prescribed many different medicines.

1 Q That's fairly comprehensive. Thank you.
2 And when you write a prescription for your
3 MS patients, for example, one of these
4 disease-modifying therapies, you include the name of
5 the drug in the prescription, correct?
6 A Of course.
7 Q The amount of medication to be dispensed to
8 the patient?
9 A Yes.
10 Q The dosing instructions for the patient?
11 A Yes.
12 Q Anything else that you include in your
13 prescriptions?
14 A Yes, sometimes.
15 Q What else would those items be?
16 A Might sometimes indicate the number of
17 refills.
18 Q Anything else?
19 A Might sometimes have directions of other
20 things to be administered with the medication.
21 Q And you just indicated that sometimes you
22 prescribe cladribine, known as Mavenclad, to your MS

1 patients, correct?
2 A That's correct.
3 Q And you are familiar with the dosing
4 regimen of Mavenclad, correct?
5 A I'm familiar with the dosing regimen, yes.
6 Q And when you write a prescription for
7 Mavenclad for one of your MS patients, you also
8 include the name of the drug, correct?
9 A Yes.
10 Q The amount of medication to be dispensed to
11 the patient, correct?
12 A No.
13 Q Dosing instructions for the patient?
14 A In the case of Mavenclad, these
15 instructions come -- come from the company.
16 Q So what do you include in a prescription of
17 Mavenclad when you write one for your patients?
18 A So we don't exactly write a prescription
19 for Mavenclad. We complete a start form.
20 Q And could you tell me what a start form is?
21 A A start form gives information to -- to the
22 company that we want to start a particular patient,

1 obviously, identify the patient, with -- with
2 Mavenclad and according to the prescribing
3 information from Mavenclad.
4 Q I'm sorry. The start form includes
5 information according to the prescribing information
6 from Mavenclad?
7 A I believe so. I don't remember off the top
8 of my head what exactly is included in a start form.
9 Q So who does the start form go to?
10 A I believe -- I believe it goes to -- to --
11 I believe it goes to EMD Serono, who is providing and
12 who makes Mavenclad.
13 Q So when you prescribe Mavenclad for one of
14 your patients, you submit a start form.
15 Is there anything else that you do in order
16 for the patient to be treated with Mavenclad?
17 A Well, I let the patient know that he or she
18 is going to receive some instructions about how
19 they -- how to take the medication.
20 Q So other than the start form, and your
21 indication to the patient that they will be receiving
22 information from the company, you do not provide any

1 other information to your patient regarding the
2 amount of medication that they will be receiving or
3 the dosing instructions for such medication?
4 DR. ELLISON: Objection. Relevance.
5 A I tell them they're going to get specific
6 information from the company.
7 Q And you don't tell them anything else
8 regarding the dosing of the drug, correct?
9 A Well, I've given them some idea of what to
10 expect, but I don't tell them the specifics.
11 Q So when you prescribe Mavenclad to your
12 patients, you don't indicate a specific dose that
13 they're going to take, correct?
14 A I don't believe that I give the specific
15 dose. But as I said, I don't recall exactly what's
16 on the start form.
17 Q Do you recall whether you include the
18 patient's weight on the start form?
19 A I believe I have to provide -- I believe
20 I'm asked to provide weight.
21 Q So either you or your colleagues then
22 determine the patient's weight so you can complete

1 the start form, correct?
2 DR. ELLISON: Objection. Form.
3 Foundation. Relevance.
4 A I believe that's the case. But as I said,
5 I don't recall the exact information that's on the
6 start form.
7 Q Before you prescribe Mavenclad to your
8 patients, you review -- strike that.
9 You've reviewed the Mavenclad label,
10 correct?
11 A Not necessarily.
12 Q The Mavenclad label is Exhibit 2001 in both
13 proceedings and let me hand that to you.
14 So this is Exhibit 2001 in both the 480 and
15 481 IPRs, and this is the Mavenclad label, or
16 otherwise known as the prescribing information for
17 Mavenclad.
18 I believe this is listed as one of the
19 documents that you considered in forming your
20 opinions, as shown at the table spanning pages 10 to
21 19 of your declaration, Exhibit 1084, as identified
22 on -- specifically on page 15.

1 A Okay.
2 Q Before prescribing Mavenclad to your
3 patients, would you have reviewed this label or
4 prescribing information?
5 DR. ELLISON: Objection. Form.
6 Foundation.
7 A At some point I would have reviewed this.
8 Q Okay. If you turn to page 3 of Exhibit
9 2001, at the bottom, the section on dosage and
10 administration starts here, correct?
11 A Yes.
12 Q And then the first subsection is Section
13 2.1, titled "Assessments Prior to Starting Each
14 Mavenclad Treatment Course." Correct?
15 A Yes.
16 Q And that subsection 2.1 starts on page 3
17 and continues to page 4, correct?
18 A 2.1?
19 Q Correct.
20 A It actually continues to page 5.
21 Q Oh, thank you.
22 And then on page 5 is the start of

1 subsection 2.2, which is "Recommended Dosage,"
2 correct?
3 A Yes.
4 Q And that subsection 2.2 continues to page
5 6, correct?
6 A Yes.
7 Q So if we look at the top of page 5, it
8 states right underneath recommended dosage, [As
9 read:] "The recommended cumulative dosage of
10 Mavenclad is 3.5 milligrams per kilogram body weight
11 administered orally and divided into two yearly
12 treatment courses (1.75 milligrams per kilogram per
13 treatment course) (see Table 1) each treatment course
14 is divided into two treatment cycles." Correct?
15 A That's correct.
16 Q And if you scroll down to the bottom of
17 that page, page 5, it states, [As read:] "Administer
18 the cycle dosage as one or two tablets once daily
19 over four to five consecutive days." Correct?
20 Sorry. I realize that actually continues
21 to the top of page 6.
22 So at the top of page 6, it states, [As

1 read:] "Administer the cycle dosage as one or two
2 tablets once daily over four or five consecutive
3 days."
4 A Of course it does say these things, but
5 these are not the way the patent under consideration
6 recommends giving cladribine.
7 Q I understand. But that's what it states,
8 correct?
9 A That is what it states here, yes.
10 Q And then it continues with [As Read:]
11 "Following the administration of two treatment
12 courses, do not administer additional Mavenclad
13 treatment during the next two years. Treatment
14 during these two years may further increase the risk
15 of malignancy, [see warnings and precautions 5.1] the
16 safety and efficacy of reinitiating Mavenclad more
17 than two years after completing two treatment courses
18 has not been studied." Correct?
19 A That's what it says.
20 Q And the passages that we just read from,
21 the subsection on recommended dosage, do not
22 expressly instruct a healthcare provider to weigh the

1 patient, correct?
2 DR. ELLISON: Objection. Relevance.
3 A These instructions clearly imply that
4 somebody had to weigh -- somebody had to weigh the
5 patient. It doesn't say who should weigh the
6 patient.
7 This is, of course, in contrast to the --
8 to the patent under discussion which had no
9 information about weighing patients.
10 Q Okay. And this subsection on recommended
11 dosage does not include any express instructions to
12 weigh the patient, correct?
13 DR. ELLISON: Objection. Relevance.
14 A Of course it's required that someone weigh
15 the patient. How can you make a dosage by patient
16 weight if somebody doesn't weigh the patient?
17 Q I can keep going. I just want to know if
18 you want to take a break or I can continue.
19 A You can continue.
20 Q Okay. Dr. Miller, your opinion is that
21 there is a subjective element to the EDSS test, due
22 to patient --

1 A Are we done with the Mavenclad label for
2 the moment?
3 Q Yes, for now. Thank you.
4 A I'm sorry I interrupted your question.
5 Q No, that's fine.
6 Your opinion is that there is a subjective
7 element to the EDSS test, due to the patient reported
8 parameters such as cognitive and mood assessment and
9 the bladder assessment, correct?
10 A Yes, I would agree with that. In some
11 elements of the EDSS, there is subjective.
12 Q And your opinion is that EDSS scoring is
13 also dependent on the examiner, correct?
14 A Yes, the EDSS score is dependent on the
15 examiner.
16 Q You conclude that the EDSS assessment, from
17 one person to the next may differ, and intra and
18 inter-rater variabilities can occur with EDSS,
19 correct?
20 A I agree with that statement.
21 Q Your opinion is that using EDSS to judge
22 efficacy is challenging, correct?

1 DR. ELLISON: Objection. Form.
2 Foundation.
3 A There are a lot of ways to judge efficacy,
4 and sometimes the use of EDSS would be challenging.
5 Q And the basis for EDSS being challenging
6 includes the intra and inter-rater variabilities,
7 correct?
8 A That would be included, among other
9 features.
10 Q And another challenge would include the
11 fact that the scale is from zero to -- strike that.
12 Another reason why EDSS would be
13 challenging is because the fact that the scale goes
14 from zero to 10 and is not linear, correct?
15 A That is a problem with the scale, that it's
16 not linear.
17 Q Another aspect that makes EDSS challenging
18 is that certain elements of the assessment are
19 subjective, correct?
20 A Yes, that is correct that some elements are
21 challenging -- are subjective.
22 Q And you would agree that because of these

1 challenges, mean EDSS isn't used anymore, correct?
2 A I would not agree with that statement.
3 Q Let's go to your second declaration,
4 Exhibit 1084 in the 480 IPR at paragraph 53.
5 A Sorry, the '947 patent second declaration,
6 right?
7 Q Correct.
8 A What page?
9 Q Let's go to page 37.
10 A Okay.
11 Q Specifically, paragraph 53.
12 A Okay.
13 Q And I'm going to ask you to count eight
14 lines down from the start of paragraph 53.
15 A The line that has "According to Dr. Lublin"
16 in it?
17 Q Correct. So that sentence states -- or at
18 that sentence, you state [As read:] "According to
19 Dr. Lublin, the challenges of using EDSS scores to
20 assess drug efficacy are why Dr. Lublin admitted that
21 we don't use things like mean EDSS anymore."
22 Your choice of the verb "admitted," you're

1 essentially agreeing that we don't use things like
2 mean EDSS anymore, correct?
3 DR. ELLISON: Objection. Form.
4 Foundation.
5 A No. I'm simply stating why Dr. Lublin said
6 that, that's his quote. I don't know if he's
7 referring to the royal "we," the papal "we" or who
8 the "we" are.
9 Q So do you agree that mean EDSS isn't used
10 anymore?
11 A No, I don't agree that it's not used.
12 Q Do you agree that mean EDSS has challenges
13 associated with it?
14 A I do agree that it has challenges with it.
15 Q Do you agree that EDSS is not ideally
16 suited to the deltas and changes in the mean that are
17 frequently used as outcome variables?
18 A I don't understand that --
19 DR. ELLISON: Objection. Foundation.
20 A I don't understand the question.
21 Q Well, would you agree that outcome
22 variables are often measured as mean changes?

1 DR. ELLISON: Objection. Foundation.
2 Form.
3 A I wouldn't agree with that statement.
4 Q Well, EDSS is measured -- or has been
5 measured as mean EDSS score, correct?
6 A Well, the term "mean EDSS score" has been
7 used, but it's not -- it's just an average of many,
8 many values. It doesn't tell us about individual
9 patients at all.
10 Q But you agree that mean EDSS has been used
11 as an outcome measure, correct?
12 A It has been used as an outcome measure by
13 some people in some studies.
14 Q And you agree that mean EDSS has challenges
15 associated with it, correct?
16 A I do agree that mean EDSS has challenges
17 associated with it.
18 Q But you don't agree that we don't use
19 things like mean EDSS anymore?
20 A There are people who continue to refer to
21 mean EDSS, so I don't agree that people don't use
22 mean EDSS.

1 Q Does mean EDSS, as an outcome measure, have
2 value as an outcome measure?
3 DR. ELLISON: Objection. Form.
4 Foundation.
5 A It might have some value, but there are
6 challenges in its use.
7 Q What are the challenges associated with
8 using mean EDSS?
9 A Well, as we've discussed, the EDSS is not a
10 linear scale, and, therefore, from a statistical
11 point of view, one is not completely valid to use a
12 mean. That's not to say that there might not be
13 some -- there might not be some utility to its use or
14 some value in its use.
15 Q You would agree that EDSS is still used as
16 an outcome measure in clinical trials for multiple
17 sclerosis, correct?
18 A Well, you have to be specific about what
19 you mean that EDSS is used as an outcome measure.
20 Q A potential -- there are several different
21 outcome measures for clinical trials for multiple
22 sclerosis, correct?

1 A There are a number of potential outcome
2 measures.
3 Q And EDSS is one of those potential outcome
4 measures, correct?
5 A Determination of EDSS is often used in some
6 way in formulating an outcome measure.
7 Q Is a determination in EDSS an important
8 outcome measure for measuring efficacy in multiple
9 sclerosis?
10 DR. ELLISON: Objection. Form.
11 Foundation.
12 A There are many ways to measure efficacy as
13 an outcome measure in multiple sclerosis. In some
14 studies, EDSS determinations might be one important
15 measure.
16 Q So despite Dr. Lublin's comment that "we
17 don't use things like mean EDSS anymore," EDSS
18 determinations might still be an important measure?
19 A I'm sure Dr. Lublin would not disagree that
20 EDSS is still an important measure referring here
21 only to mean EDSS measures.
22 Q Would you agree that EDSS is the criterion

1 standard by which disability in multiple sclerosis
2 patients is measured?
3 A Would you please define how you're using
4 the term "criterion standard."
5 Q What is your understanding of the term
6 "criterion standard"?
7 A Well, my understanding of the term would be
8 a measure that's most frequently used by experts in
9 the field. So I would say that the EDSS is the most
10 widely used measure of disability, despite the fact
11 that it has many flaws.
12 Q And by 2004, EDSS had been used as a
13 primary outcome measure in clinical trials studying
14 multiple sclerosis drugs, correct?
15 A EDSS itself is not the outcome measure.
16 EDSS is a measure. You have to apply something that
17 you want to know about the EDSS. EDSS was widely
18 used.
19 Q Could you explain further when you say "you
20 have to apply something that you want to know about
21 the EDSS"?
22 A Well, I can give you an example.

1 Q Please.
2 A One measure might be to look at how many
3 people, what percentage of patients had a change in
4 their EDSS. And usually we'd look at a confirmed
5 change, meaning it wasn't seen on just one
6 examination.
7 Q And when you say it wasn't just seen on one
8 examination, do you mean it was seen on multiple
9 examinations?
10 A When -- when we use the term confirmed --
11 "confirmed disability progression," meaning a
12 confirmed change in the EDSS that had to have been
13 seen on multiple occasions.
14 Q And how frequently would you measure EDSS
15 to get to a confirmed disability progression?
16 A Well, this would be variable from trial to
17 trial. But usually it means at least three -- in at
18 least at a second examination three months later,
19 sometimes you look at a second examination six months
20 later.
21 Q So let's just use your example of one way
22 in which EDSS is used to measure an outcome. And

1 let's say that that example that you just set forth
2 is the primary outcome measure for a given multiple
3 sclerosis study.
4 If that primary outcome measure isn't met,
5 what conclusions could a clinician draw about the
6 efficacy of that multiple sclerosis drug being
7 studied?
8 A You could draw the conclusion that the
9 primary outcome measure wasn't met.
10 Q Are there any conclusions that could be
11 drawn about the efficacy of the multiple sclerosis
12 drug that was being studied?
13 DR. ELLISON: Objection. Foundation.
14 Q Based on that primary outcome measure?
15 DR. ELLISON: Objection. Foundation.
16 A Please repeat the question.
17 Q Would a clinician be able to draw any
18 conclusions about the efficacy of that multiple
19 sclerosis drug based on the primary outcome measure
20 not being met?
21 DR. ELLISON: Objection. Foundation.
22 A One could conclude that in that particular

1 trial, the primary efficacy measure was not met, and,
2 therefore, the trial did not prove efficacy for the
3 drug in that trial.
4 Q Assuming that same clinical study has a
5 secondary outcome measure where that secondary
6 outcome measure was met, but the primary outcome
7 measure was not met, what conclusions could a
8 clinician draw about the efficacy of that multiple
9 sclerosis drug, based on the primary outcome measure
10 not being met?
11 DR. ELLISON: Objection. Foundation.
12 A Well, I'm not sure that a clinician could
13 draw a conclusion in that circumstance. The
14 physician interpreting that data would have -- would
15 have seen that the study had shown some evidence of
16 efficacy on some measures, but not evidence of
17 efficacy on the primary measure.
18 Q And what if it were the other way around --
19 strike that.
20 Would your answer be the same with respect
21 to whether or not a physician or a clinician could
22 draw any conclusions with respect to the efficacy of

1 that multiple sclerosis drug based on the secondary
2 outcome measure being met but the primary outcome
3 measure not being met?
4 A If the primary efficacy outcome measure had
5 not been met but the secondary measures were met, the
6 person interpreting that trial would have concluded
7 that the trial itself had been unsuccessful in
8 meeting its primary end point, but there might be
9 some suggestion that the drug still had efficacy,
10 based on the secondary endpoints.
11 Q When you say that there could be "some
12 suggestion that the drug still had efficacy, based on
13 secondary endpoints," would you consider that
14 suggestion to be a hypothesis-generating suggestion?
15 DR. ELLISON: Objection. Form.
16 Foundation.
17 A So a drug can have many potential effects
18 -- speaking of multiple sclerosis, specifically, a
19 drug can have many effects. So a primary endpoint
20 might not be reached because the drug might have
21 other effects so that the secondary endpoints could
22 be -- could be very important as measures of efficacy

1 and that might lead to the generation of new trials
2 eventually.
3 Q So going back to your comment that there's
4 some suggestion that the drug still had efficacy
5 based on secondary endpoints, when you say
6 "suggestion," do you mean that that is a conclusion
7 that can be drawn with respect to the efficacy of
8 that drug?
9 DR. ELLISON: Objection. Form.
10 Foundation.
11 A We -- we often don't reach firm conclusions
12 based on a single trial. We look at all the evidence
13 that we have available to us in judging the efficacy
14 of a drug.
15 Q Dr. Miller, your opinion is that a
16 reduction in relapse rate is important in determining
17 clinical efficacy of an MS drug, and, therefore, it
18 is included in almost all MS trials as an endpoint,
19 correct?
20 A If the trial is of a disease-modifying
21 agent, then usually relapse rate is usually one of
22 the parameters that's included. There are many

1 measures -- there are many measures of efficacy, and
2 depends on the stage of the trial, what kind of trial
3 it is. But relapse reduction is a very frequently
4 used measure of efficacy.
5 Q And specifically, relapse reduction is an
6 important measure in determining clinical efficacy of
7 an MS drug, correct?
8 DR. ELLISON: Objection. Form.
9 Foundation.
10 A Relapse rate reduction is one of a number
11 of potential measures of efficacy in clinical trials.
12 Q And specifically, a reduction in relapse
13 rate is an important outcome measure in determining
14 clinical efficacy of a multiple sclerosis drug,
15 correct?
16 DR. ELLISON: Objection. Form.
17 Foundation.
18 A In some clinical trials.
19 Q In clinical trials for disease-modifying
20 therapies?
21 DR. ELLISON: Objection.
22 A In some clinical trials.

1 Q And you agree that relapse rate is
2 typically measured over one year?
3 A It's a variable.
4 Q So in your opinion, relapse rate could be
5 measured in less than one year?
6 A It could be.
7 Q And it could also be measured longer than
8 one year?
9 A It could be.
10 Q And your opinion is that relapse rate is a
11 routine measure of disease activity that is easy to
12 quantify, correct?
13 A Well, I -- I'm not sure what you mean by
14 "routine measure," but it is -- it is reasonably --
15 it is reasonably easy to measure and quantify. There
16 are some confounding issues, but...
17 Q What are those confounding issues?
18 A You would have to have a clear definition
19 of -- in a clinical trial, you have to have a clear
20 definition of how you're determining that somebody
21 has had a relapse. Depends in part on who's making
22 the determination that a person has had a relapse.

1 Q So you would agree that relapse rate, like
2 EDSS, includes subjective elements, correct?
3 A I wouldn't necessarily agree with that
4 statement.
5 Q So in determining whether or not a patient
6 has had a relapse, you stated that it depends in part
7 on who's making the determination that a person has
8 had a relapse. In your opinion, does that not make
9 determining relapse rate a subjective process?
10 DR. ELLISON: Objection. Form.
11 Foundation.
12 A I'm not sure how you're using the term
13 "subjective process."
14 Q Well, would having a -- strike that.
15 There are subjective elements to measuring
16 relapse rate, given that determining whether or not
17 somebody has a relapse depends on who's making the
18 determination that a person has had a relapse,
19 correct?
20 A In determining -- in determining relapse
21 rate in a clinical trial, you have to have a specific
22 definition of a relapse.

1 Q And that -- strike that.
2 And that definition of a relapse can vary
3 from trial to trial, correct?
4 A That's correct.
5 Q And you depend on patients to initially
6 report the relapse, correct?
7 A By -- by most definitions, the
8 determination of a relapse is dependent on a patient
9 reporting some symptoms, so the patient is always
10 involved.
11 Q And thus, that makes determining whether or
12 not a relapse has occurred a subjective process,
13 correct?
14 A Well, I still don't understand what you
15 mean by "a subjective process." If you're saying
16 that any -- any time a patient says something, then
17 it's a subjective process, then, yes, it's a
18 subjective process. But assuming the patient is
19 reporting a symptom, then it's not necessarily a
20 subjective process.
21 Q Well, would you say there are certain
22 elements of assessing relapse rate that would be

1 subjective?
2 A Possibly.
3 Q For example, patients cannot always
4 distinguish a true exacerbation from a
5 pseudoexacerbation, correct?
6 A A patient often doesn't know what is meant
7 by a pseudoexacerbation.
8 Q And the determination of a relapse is often
9 left to the investigator's judgment to interpret,
10 correct?
11 A It is sometimes left to the examiner's
12 judgment.
13 Q Would you agree that even with the most
14 rigorous definition for relapse, that borderline
15 events will always be left to the investigator's
16 judgment to interpret?
17 DR. ELLISON: Objection. Form.
18 Foundation.
19 A I wouldn't agree with that statement as
20 made.
21 Q Would you agree that relapse rate is a
22 useful but flawed measure of multiple sclerosis

1 disease activity?
2 DR. ELLISON: Objection. Foundation.
3 A Please reread the question.
4 Q Would you agree that relapse rate is a
5 useful but flawed measure of multiple sclerosis
6 disease activity?
7 DR. ELLISON: Objection. Foundation.
8 A Well, no measure -- no measures are ever --
9 are ever perfect when you're doing clinical
10 examinations and taking clinical histories. But a
11 relapse rate is generally regarded as a fairly
12 reliable measure of efficacy, changes in -- changes
13 in relapse rate.
14 Q It's also a flawed measure of MS disease
15 activity, correct?
16 A As I said, you can apply the term "flawed
17 measure" to any measure. Nothing is perfect in
18 clinical medicine.
19 Q So Stelmasiak, which we discussed in
20 Exhibit 1013, measured relapse rate, correct?
21 A Stelmasiak did measure relapse rate, yes.
22 Q And your opinion is that Stelmasiak had a

very marked reduction in relapse rate during the two years after the initiation of the treatment, correct?

A Yes, in many of the patients.

Q You agree that Stelmasiak's trial was performed with a small number of patients and was not placebo controlled, and as such, its results concerning the efficacy of treatment shall, therefore, be interpreted with great caution?

A I believe Stelmasiak himself said that, and I do agree that it was a small number of patients, and I do agree that it was not placebo controlled.

Q Do you agree that its results concerning the efficacy of the treatment shall, therefore, be interpreted with great caution?

A Results of any clinical trial should be interpreted with caution.

Q Including Stelmasiak's, correct?

A Any clinical trial should be interpreted with caution.

Q You would agree that when studying an agent in a multiple sclerosis clinical trial, a study must be of sufficient duration to allow the benefit of the

1 agent to become evident and have a subject population
2 large enough to power the study adequately?
3 DR. ELLISON: Objection. Foundation.
4 A It depends.
5 Q What would that depend on?
6 DR. ELLISON: Objection. Foundation.
7 A It depends on the goal of the trial.
8 Q And if the goal of the trial is to
9 determine the benefit of that agent, would that study
10 have to be of sufficient duration to demonstrate that
11 benefit?
12 A Depends on -- depends on the trials, the
13 stage of the testing.
14 Q Are you saying that some trials need not
15 have sufficient duration to determine the benefit of
16 that agent?
17 DR. ELLISON: Objection. Form.
18 Foundation.
19 A Well, it would determine the apparent
20 benefit of an agent in that trial.
21 Q So to determine the apparent benefit of an
22 agent in that trial, that trial must be of sufficient

1 duration, correct?
2 A A trial -- a trial must be of sufficient
3 duration and numbers to be able to answer the
4 question that the trial was trying to answer.
5 Q You would agree that for multiple sclerosis
6 trials, short-term trials are usually between one and
7 three years in duration?
8 A I wouldn't necessarily agree with that
9 statement.
10 Q What would the duration of a short-term
11 trial be for multiple sclerosis?
12 A It's highly variable.
13 Q What would it depend on?
14 A The design -- the design of the trial and
15 the question that one wanted to answer.
16 Q So it could be between one and three years?
17 A What are you asking specifically?
18 Q Sorry. For multiple sclerosis trials, a
19 short-term trial could be between one and three years
20 in duration?
21 A A short-term trial in multiple sclerosis
22 could be of varying lengths, including one to three

1 years, but not necessarily for that length.
2 DR. KAN: I'm going to introduce a new
3 exhibit marked as 2077. Just bear with me.
4 DR. ELLISON: Counsel, is it possible for
5 you to put a copy of the exhibit in the chat?
6 DR. KAN: I can. I'm going to have to log
7 into my computer, and I don't -- I don't know if we
8 have the same upload/download link because we asked
9 for an upload link but we didn't end up using it, and
10 one wasn't sent separate of that, so...
11 DR. ELLISON: Is it possible for you to
12 send a PDF to either me or to Ms. Partington, so we
13 can -- so she can have a copy of it during this
14 deposition?
15 DR. KAN: Yes. Do you want to go off
16 record and take a break so I can do that?
17 DR. ELLISON: That would be great, yes.
18 Thank you.
19 DR. KAN: Okay. We'll go off record.
20 (Recess 11:45 a.m. - 1:03 p.m.)
21 (Miller Exhibit 2077 marked for
22 identification.)

1 BY DR. KAN:
2 Q Okay. Dr. Miller, before we went on a
3 break, you indicated that you disagreed that for
4 multiple sclerosis short-term trials are usually
5 between one and three years in duration, correct?
6 DR. ELLISON: Objection. Form.
7 Foundation.
8 A I'm not sure that that's exactly what I
9 said, but the duration of short-term trials is
10 extremely variable, and I can't tell you what
11 percentage of them are between one and three years
12 and what percentage are shorter, but there are many
13 trials that are shorter than one to three years.
14 Q Okay. I'm going to turn to Exhibit 2077,
15 which we marked prior to the break and which I
16 believe you have a copy and counsel also has a copy.
17 Do you recognize Exhibit 2077, Dr. Miller?
18 A I do.
19 Q This is a book chapter that you wrote that
20 was published back in 2011, correct?
21 A Yes.
22 Q And the title of the book is "Primer On

1 Multiple Sclerosis," correct?
2 A Yes.
3 Q And the specific book chapter authored by
4 you, co-authored by you, is titled "Issues in the
5 Design and Interpretation of Multiple Sclerosis
6 Clinical Trials." Correct?
7 A Yes.
8 Q And if you would turn to page 436 of
9 Exhibit 2077, in the right column, last paragraph,
10 there's a header "Short-Term, Relapse-Based
11 Outcomes." Correct?
12 A Yes.
13 Q And the second sentence in that paragraph
14 states, "As short-term trials (usually between 1 and
15 3 years in duration) are often underpowered to
16 demonstrate effect on long-term disability, endpoints
17 such as the annualized relapse rate, time to first
18 relapse, and percent of patients relapse-free serve
19 as surrogate markers of disease suppression."
20 Correct?
21 A Yes.
22 Q So this was a true and accurate statement

1 when you published it in 2011?
2 A So I think we were referring here mainly --
3 or considering mainly in terms of phase 3 trials,
4 because the latter part of the paragraph refers to
5 placebo-controlled trials, which most often are
6 those. So this statement is proving a relationship
7 to those, but other -- other trials can be much
8 shorter.
9 Q When you say "other trials," you mean phase
10 2 and phase 1 trials?
11 A Phase 1, phase 2 trials, yes.
12 Q I think earlier we were also talking about
13 assessing relapse rates and we had talked about
14 whether or not there was a subjective element to
15 interpreting -- or to assessing relapse rates, sorry,
16 and you disagreed that even with the most rigorous
17 relapse criteria, borderline events will always be
18 left to investigator's judgment to interpret,
19 correct?
20 DR. ELLISON: Objection. Form.
21 Foundation.
22 A You would have to go back and read me the

1 exact question, because I can't remember now.
2 Q Well, do you agree that even with the most
3 rigorous relapse criteria, borderline events will
4 always be left to the investigator's judgment to
5 interpret?
6 A I see. No, I don't agree with that
7 statement.
8 Q Could you turn to page 427 of Exhibit 2077.
9 In the left column, second full paragraph,
10 if you scroll down to the second-to-last sentence, so
11 I would say seven lines up from the bottom, you
12 wrote, "Even with the most rigorous relapse criteria,
13 borderline events will always be left to the
14 investigator's judgment to interpret." Correct?
15 A That's what the statement says, yes.
16 Q That was a true and accurate statement when
17 you published it in 2011?
18 A Well, that's -- that's a true statement,
19 but in a clinical trial, and not all relapses are
20 ultimately determined by the investigator.
21 Q If they are not ultimately determined by
22 the investigator, are they determined by the patient?

1 A They are usually not -- they're usually not
2 determined by the patient.
3 Q So if they're neither determined by the
4 investigator nor the patient, who are they determined
5 by?
6 A Sometimes there's an adjudication committee
7 that determines whether a relapse was to be counted
8 as a relapse.
9 Q So given that relapses may be determined by
10 either the investigator, the patient, or an
11 adjudication committee, would you agree that there is
12 a subjective element to assessing relapses?
13 A I wouldn't agree because I didn't say that
14 relapses could be determined by the patients.
15 Q Would you agree that many trials rely on
16 patients to report the occurrence of a relapse?
17 A I wouldn't agree with the statement as you
18 put it.
19 Q So staying on page 437 of Exhibit 2077,
20 left column, first full paragraph, the last sentence,
21 you wrote, "Patients cannot always distinguish a
22 true" --

1 A Hold on. I'm lost. Where is that?
2 Q Page 437, left column, first full
3 paragraph.
4 A Left column, first paragraph. "Patient
5 cannot" -- I get it.
6 Q You wrote, "Patients cannot always
7 distinguish a true exacerbation from a
8 pseudoexacerbation, which is significant given that
9 many trials rely on patients to report occurrence of
10 a relapse."
11 A So what I mean here is patients report
12 symptoms which triggers the assessment of whether a
13 relapse has occurred. Relapses are not counted by
14 what -- by whether the patient says they're having a
15 relapse, at least hardly ever, if ever.
16 Q Do investigators rely on these symptoms to
17 determine whether or not there is a relapse?
18 A As I previously said, in most trials,
19 consideration of whether a relapse has occurred
20 depends on whether the patient reports some -- some
21 symptoms.
22 Q And so investigators report on these

1 symptoms -- strike that.
2 Investigators rely on these symptoms as
3 reported by the patient, correct?
4 DR. ELLISON: Objection. Form.
5 Foundation.
6 A Doctors always listen and hear what the
7 patient says.
8 Q And because the symptoms are reported by
9 the patients, that leads to a subjective element
10 during the assessment process, correct?
11 A As I said earlier, any time you're hearing
12 something from a patient, you could regard it as
13 subjective because it's not an observation you're
14 making yourself.
15 Q Okay. You can put aside Exhibit 2077 for
16 now. I'm going to hand you what has been previously
17 marked as Exhibit 2017 in both the 480 and 481 IPRs.
18 Exhibit 2017 is the Copaxone,
19 C-o-p-a-x-o-n-e, package insert, correct?
20 A I think so. It's not labeled as such, but
21 I believe that's the case.
22 Q Okay. Well, this is how it's identified in

1 your -- in the table in your declaration, Exhibit
2 1084 --
3 A Okay.
4 Q -- at page 16, so, and you --
5 A I accept it.
6 Q Okay. And you considered Exhibit 2017 in
7 forming your opinions for your second declaration,
8 correct?
9 A Yes.
10 Q I'm also going to note that in your
11 declaration, that table referring to Exhibit 2017 on
12 page 16 notes that the package insert (since 2001).
13 So in 2004, the FDA-approved dose for
14 Copaxone was 20 milligrams per day, correct?
15 A I believe that's correct.
16 Q So, for example, at page 19 of Exhibit
17 2017, under Dosage and Administration, it states,
18 "The recommended dose of Copaxone for the treatment
19 of RRMS is 20 milligrams per day injected
20 subcutaneously."
21 A Yes.
22 Q And the generic name for Copaxone is

1 glatiramer acetate, correct?
2 A Yes.
3 Q G-l-a-t-i-r-a-m-e-r, a-c-e-t-a-t-e.
4 So when I refer to the page numbers in this
5 document, I'm going to be referring to the native
6 page numbering at the top left corner. And if you
7 turn to page 4 of Exhibit 2017, there's a header of
8 "Clinical Trials." Correct?
9 A Yes.
10 Q And if you continue to page 6, we're still
11 in the clinical trials section, correct?
12 A Yes.
13 Q On page 6, the second paragraph states, "A
14 third study was a multinational study in which MRI
15 parameters were used as primary and secondary
16 endpoints. A total of 239 patients with RRMS (119 on
17 glatiramer acetate and 120 on placebo) were
18 randomized. The patients were treated in a double
19 blind manner for nine months during which they
20 underwent monthly MRI scanning." Correct?
21 DR. ELLISON: Objection. Form.
22 Foundation.

1 A You read correctly what's written there.
2 Q And then that paragraph continues with "The
3 primary endpoint for the double-blind phase was the
4 total cumulative number of T1 gadolinium-enhancing
5 lesions over the nine months. Table 3 summarizes the
6 result for the primary outcome measures monitored
7 during the trial for the intent to treat cohort."
8 Correct?
9 A Yes.
10 Q Now, if you turn to page 7, there's a
11 Figure 1 located there, correct?
12 A Yes.
13 Q The figure is titled "Median Cumulative
14 Number of Gadolinium-Enhancing Lesions." Correct?
15 A Yes.
16 Q So over the nine-month period for the
17 patients treated with Copaxone, the median cumulative
18 number of gadolinium-enhancing lesions was about 11,
19 correct?
20 A Yes.
21 Q The baseline number of gadolinium-enhancing
22 lesions was zero, correct?

1 A Yes.
2 Q So the Copaxone treated group had an
3 increase in the number of gadolinium-enhancing
4 lesions from zero to 11, correct?
5 DR. ELLISON: Objection. Relevance.
6 A Well, you're not posing the question in a
7 reasonable way. Zero is -- zero is the result on one
8 scan. The 11 is on -- is on 9 or 10 scans. They are
9 doing monthly scans.
10 So of course, there are going to be more
11 lesions on -- if you get any lesions, there's always
12 going to be more lesions than at the baseline because
13 you're starting with zero. And I would have to look
14 back at that particular reference, but it's likely
15 that it was required that you couldn't have any
16 gadolinium-enhancing lesions on the initial scan. So
17 what you're asking me is not making any sense.
18 Q Well, over the nine-month period during
19 which the patients in the Copaxone treated group had
20 numerous scans, they started with zero
21 gadolinium-enhancing lesions at baseline, and the
22 mean cumulative number of gadolinium-enhancing

1 lesions at month 9 was approximately 11, correct?
2 A That's an inaccurate statement.
3 Q How would you frame the change in
4 cumulative number of enhancing lesions for the
5 Copaxone treated group --
6 DR. ELLISON: Objection.
7 Q -- over the nine-month period?
8 DR. ELLISON: Objection. Form.
9 Foundation. Scope.
10 A Re-ask your question, please.
11 Q How would you frame the change in
12 cumulative number of enhancing lesions for the
13 Copaxone treated group over the nine-month period?
14 A That doesn't require any interpretation.
15 There were -- there was a median of 11 lesions
16 developing over the nine months. There have to be
17 zero lesions at baseline. The cumulative value at
18 baseline has to be zero.
19 Q Okay. So there was a median of 11 lesions
20 developing over the nine months, correct?
21 A That's correct. You asked me about the
22 mean before and this is a median.

1 Q So if the patients had an increase in the
2 median number of gadolinium-enhancing lesions, that
3 means they are getting worse, correct?
4 A No, not necessarily.
5 Q Is the number of gadolinium-enhancing
6 lesions a measure of inflammation in multiple
7 sclerosis?
8 A It's not a measure of inflammation.
9 Q But you can infer inflammation from the
10 number of gadolinium-enhancing lesions, correct?
11 A One infers that there is inflammation when
12 one sees a gadolinium-enhanced lesion.
13 Q So if the median must be of
14 gadolinium-enhancing lesions increases, and patients
15 are not getting worse, what conclusions could a
16 clinician draw about those gadolinium-enhancing
17 lesions?
18 DR. ELLISON: Objection. Form.
19 Foundation.
20 A It could infer that the patient is getting
21 better, staying the same, or getting worse.
22 Q So is it your opinion that for patient

1 cohort, when the median number of
2 gadolinium-enhancing lesions increases, those
3 patients could be getting better?
4 A Or staying the same or getting worse.
5 Q So in your opinion, looking at Figure 1 for
6 this clinical trial that's included in the Copaxone
7 package insert, what conclusions could you draw about
8 the efficacy of Copaxone for treating multiple
9 sclerosis?
10 DR. ELLISON: Objection. Form. Scope.
11 A I can interpret from looking at Figure 1
12 that the patients on Copaxone developed fewer
13 gadolinium-enhanced lesions than the people who were
14 taking placebo over a nine-month period.
15 Q What conclusions can you make, based on
16 your observation, that the Copaxone treated group
17 developed fewer gadolinium-enhanced lesions as
18 compared to placebo over the nine-month period?
19 DR. ELLISON: Objection. Scope.
20 A I think I just answered that question. I'd
21 say in the nine-month period that the group taking
22 Copaxone developed fewer lesions than the group

1 taking placebo.
2 Q And there are no other conclusions you can
3 draw from that?
4 DR. ELLISON: Objection. Scope.
5 A I can't draw any other conclusions from
6 that.
7 Q If you take a look at month 9, the Figure
8 1, both the placebo group and the Copaxone group
9 developed the same number of gadolinium-enhancing
10 lesions, correct?
11 A No, that's not true.
12 Q The median number of gadolinium-enhancing
13 lesions was the same for both the placebo group and
14 the Copaxone group at month 1, correct?
15 A Oh, at month 1. I thought you said at
16 month 9.
17 Q No.
18 A I apologize. At month 1 the median numbers
19 were the same, yes.
20 Q And it looks like both groups had
21 approximately two gadolinium-enhancing lesions,
22 correct?

1 A Both groups had a median of about two, yes.
2 Q What conclusions, if any, can you draw
3 about the efficacy of the Copaxone treatment based on
4 the data for month 1 here?
5 A Nothing.
6 Q And if you take a look at month 2, the
7 Copaxone group appears to have developed a greater
8 number of gadolinium-enhancing lesions compared to
9 the placebo group, correct?
10 DR. ELLISON: Objection. Form.
11 Foundation. Scope.
12 A There was a higher -- there was a higher
13 median number in the Copaxone group than in the
14 placebo group, yes.
15 Q What conclusions, if any, can you draw
16 about the efficacy of the Copaxone treatment based on
17 the data for month 2 here?
18 A I can't draw any conclusions.
19 Q And if you look at month 3, the median
20 number of gadolinium-enhancing lesions was the same
21 for both the placebo group and the Copaxone group,
22 correct?

1 A Yes.
2 Q And what conclusions, if any, can you draw
3 about the efficacy of the Copaxone treatment based on
4 the data for month 3?
5 A None.
6 Q What conclusions, if any, can you draw
7 about the efficacy of the Copaxone treatment based on
8 the data at month 9?
9 A At month 9, I can conclude that there are
10 fewer -- a median of fewer lesions developing in the
11 Copaxone group than in the placebo group.
12 Q And so you can't draw any conclusions about
13 the efficacy of the Copaxone treatment at month 9,
14 correct?
15 A I can't draw a firm conclusion. It's one
16 bit of data.
17 Q This clinical study that we've been
18 referring to or studying, has -- had 239 patients
19 enrolled, correct?
20 A Yes.
21 Q Could this study have been done with one
22 patient?

1 A No.
2 Q Why not?
3 A Well, it's a placebo-controlled trial,
4 which means you're comparing an active treatment to a
5 placebo treatment. That requires at least two
6 patients to have been in the trial.
7 Q So this study could have been done with two
8 patients then?
9 A It could have been done with two patients.
10 Q So in this study, the MRI parameters were
11 used both as primary and secondary endpoints. The
12 only results provided are the medians of the
13 cumulative number of T1 gadolinium-enhancing lesions.
14 Do you agree that this study required a
15 large enough patient population to be able to
16 determine whether the difference in MRI outcomes for
17 the two populations is actual as opposed to by
18 chance?
19 DR. ELLISON: Objection. Form.
20 Foundation.
21 A That question doesn't make any sense.
22 Q Would you agree that when you design a

1 clinical trial, you design it around an outcome
2 measure that you're interested in, and so the design
3 and statistics are set up to answer that question
4 with respect to that outcome measure?
5 A Yes, I would agree with that.
6 Q And so with respect to this clinical trial
7 that we just discussed in the Copaxone study or the
8 Copaxone label, that clinical trial was designed
9 around MRI parameters, correct?
10 DR. ELLISON: Objection. Scope.
11 Foundation.
12 A Yes, it was.
13 Q And that study required a large enough
14 population to determine whether or not the difference
15 in outcomes for the two populations is real, correct?
16 DR. ELLISON: Objection. Foundation.
17 A That's not necessarily so.
18 Q Do you agree that there would be a minimum
19 patient population required to determine whether or
20 not the difference in outcomes for the two
21 populations is real?
22 DR. ELLISON: Objection. Foundation.

1 A Not necessarily so.
2 Q How many patients would you need to
3 determine whether or not the difference in MRI
4 parameters -- strike that.
5 How many patients would you need to
6 determine whether or not the difference in MRI
7 outcomes for the two populations is real?
8 DR. ELLISON: Objection. Form.
9 Foundation.
10 A I don't know what you mean by "real."
11 Q Well, it's possible that some patients will
12 develop gadolinium-enhancing lesions, regardless of
13 whether they are in the treated group or the
14 untreated group, correct?
15 A That is likely to be true.
16 Q So when I say "real," how do you know that
17 any observed effect is actually the effect of
18 Copaxone treatment as opposed to just the normal
19 progression of the disease?
20 A I don't know what you mean by "real." They
21 counted lesions. The lesions are presumably
22 accurately counted, and, therefore, the different --

1 the numbers are real.
2 Q How do you know that any observed effect is
3 actually the effect of Copaxone, as opposed to just
4 normal progression of the disease?
5 A You don't know for sure.
6 Q Is there any way to know for sure?
7 A No.
8 Q Okay. Please turn to page 5 of Exhibit
9 2017, so we're still in the same exhibit.
10 A Page 5?
11 Q Yes.
12 A Okay.
13 Q The sole paragraph on page 5 states, [As
14 read:] "The second trial was a multi-center trial of
15 similar design which was performed in 11 US centers.
16 A total of 251 patients (glatiramer acetate, 125;
17 placebo, 126) were enrolled. The primary outcome
18 measure was the mean two-year relapse rate. The
19 table below represents the values of this outcome for
20 the intent to treat population, as well as several
21 secondary measures." Correct?
22 A Yes, that's what it says.

1 Q And when it says "the table below," it's
2 referring to Table 2 on page 6, correct?
3 A Correct.
4 Q Okay. And this Table 2 is titled "Study 2
5 Efficacy Results." Correct?
6 A Correct.
7 Q Table 2 shows five different outcome
8 measures, correct?
9 A Correct.
10 Q The first outcome measure, mean number of
11 relapses, is the primary outcome measure, correct?
12 A Yes.
13 Q And the other four outcome measures are
14 secondary outcome measures, correct?
15 A I don't know. It doesn't say what they
16 were. It only says, in the previous sentence, that
17 the primary outcome measure -- although it does say
18 "as several secondary measures." It doesn't say
19 whether -- it doesn't say whether these are all
20 secondary measures.
21 Q It suggests that these other measures are
22 secondary outcome measures, correct?

1 A I would agree, yes.
2 Q So looking at Table 2, the mean number of
3 relapses, the glatiramer acetate group had an average
4 1.19 relapses over two years, whereas the placebo
5 group had 1.68 relapses over two years, correct?
6 A Yes.
7 Q So on average, the glatiramer acetate group
8 had fewer lapses, correct?
9 A Correct.
10 Q In your opinion, these results indicate
11 that glatiramer acetate was more effective than
12 placebo in reducing the number of relapses, correct?
13 A Possibly.
14 Q Looking at the percentage of patients who
15 were relapse-free, 34 percent of the patients in the
16 glatiramer acetate group were relapse-free, as
17 compared to 27 percent of the patients in the placebo
18 group, correct?
19 A Correct.
20 Q So the glatiramer acetate group had a
21 higher percentage of patients who were relapse-free,
22 correct?

1 A Correct, but not statistically
2 significantly so.
3 Q In your opinion, do these results indicate
4 that glatiramer acetate was more effective than
5 placebo in keeping patients relapse-free?
6 A They don't tell me that with any degree of
7 certainty. Even the mean number of relapses did
8 not -- did not quite meet traditional levels of
9 statistical significance.
10 Q And when you say "the mean number of
11 relapses did not quite meet traditional levels of
12 statistical significance," is that because the P
13 value is 0.055?
14 A Yes.
15 Q And would traditional levels of statistical
16 significance be P value 0.05 or less?
17 A Almost all studies use even lower values
18 than that, but it's very rare that -- especially a
19 phase 3 trial would rely on a statistical value that
20 was greater than .05.
21 Q Okay. So then looking at the percent --
22 percentage of patients who were relapse-free, even

1 though 34 percent of the patients in the glatiramer
2 acetate group were relapse-free, as compared to 27
3 percent of the patients in the placebo group, the
4 results do not indicate with statistical significance
5 that the glatiramer acetate group was more
6 effectively treated than the placebo group, correct?
7 A Correct. It's not clear that -- it's not
8 clear that there was a difference.
9 Q And then if we go to the median time, the
10 first relapse, the median time of first relapse was
11 longer in the glatiramer acetate group at 287 days,
12 as compared to 198 days in the placebo group,
13 correct?
14 A Yes.
15 Q And do these results indicate that
16 glatiramer acetate was more effective than placebo in
17 preventing relapses for a longer period of time?
18 A The confidence level was not great enough
19 to draw that conclusion because the P value was .23.
20 Q And then if we look at the percentage of
21 patients who were progression-free, 78 percent of the
22 patients in the glatiramer acetate group were

1 progression-free, as compared to 75 percent of the
2 patients in the placebo group, correct?
3 A That's correct.
4 Q And so the glatiramer acetate group had a
5 higher percentage of patients who were
6 progression-free, correct?
7 A Slightly higher percentage, yes.
8 Q And in your opinion, what do these results
9 indicate -- strike that.
10 In your opinion, do these results indicate
11 that glatiramer acetate was more effective than
12 placebo in keeping patients progression-free?
13 DR. ELLISON: Objection. Scope.
14 A I would not be able to draw that
15 conclusion.
16 Q Why not?
17 DR. ELLISON: Objection. Scope.
18 A Because the P value, and hence, the
19 confidence level that this is an effective difference
20 between the two arms of the study is not -- is not
21 met.
22 Q And looking at the last outcome measure of

1 mean change in DSS. What is DSS?
2 A DSS stands for Disability Status Scale
3 score. It was an antecedent to the EDSS, which is
4 the Expanded Disability Status Scale. DSS is a
5 10-point scale without half steps, whereas the EDSS
6 has half steps at all levels except zero to 1.
7 Q So DSS is, likewise, a measure of
8 disability progression then?
9 A Yes.
10 Q And if we look at the mean change in DSS,
11 the glatiramer acetate group had a negative change of
12 0.5, while the placebo group had a positive change of
13 0.21, correct?
14 A Yes.
15 Q A negative change in DSS score indicates an
16 improvement in disease progression, correct?
17 A Well, again, these are mean changes, so you
18 can't make most of the -- in an individual patient,
19 the lower EDSS score would mean improvement.
20 Q Would you be able to draw any conclusions
21 about the glatiramer acetate group based on the mean
22 change in DSS?

1 A Well, these comparisons had what would be
2 conventionally acceptable to be a reasonable P value.
3 So it would tell us that there was a relatively small
4 chance that these findings could have happened by
5 chance. So it's suggestive that glatiramer acetate
6 was having an impact in reducing the progression of
7 disability, but it's not absolute proof of that.
8 Q Okay. So then for the placebo group, where
9 there was a positive change in DSS, in mean DSS,
10 would you agree that that indicates that the placebo
11 group had a worsening of disease progression?
12 A On average, again, the group had a
13 worsening of disease progression.
14 Q So on average, the glatiramer acetate group
15 had an improvement in disease progression, as
16 compared to the placebo group, correct?
17 A That's correct.
18 Q And these results would indicate that the
19 glatiramer acetate was more effective than placebo in
20 improving disease progression, correct?
21 A I can't interpret your use of the word
22 "improving disease progression."

1 Q Okay. Let me rephrase that.
2 These results would indicate that the
3 glatiramer acetate was more effective than placebo in
4 reducing the progression of disability, correct?
5 A On average, yes.
6 Q Would you agree that all five of these
7 outcome measures point to the same general effect
8 that glatiramer acetate is effective in achieving the
9 designated outcomes as compared to placebo?
10 A I would not agree with that statement.
11 Q And you would not agree with that statement
12 because of the P values?
13 A Yes.
14 Q Is there any other reason why you would not
15 agree with that statement?
16 A Could you reread your original question
17 about this?
18 Q My original question was would you agree
19 that all five of these outcome measures point to the
20 same general effect that glatiramer acetate is
21 effective in achieving designated outcomes as
22 compared to placebo?

1 A So I would not agree that they all -- that
2 they all point to that, and mainly it's because you
3 can't even get any firm impression of improvement
4 from the second, third, and fourth outcome measures.
5 Q In your opinion, did the results of study 2
6 support the efficacy of glatiramer acetate in
7 treating RRMS patients?
8 A Well, I would say that they -- they suggest
9 the efficacy. They don't -- but not conclusively so.
10 Q In your opinion, in the MS study is it
11 important that the designated outcome measures point
12 to the same general effect?
13 DR. ELLISON: Objection. Form.
14 Foundation.
15 A When that -- when that happens, it gives
16 one greater confidence in the -- in the outcome, in
17 the efficacy.
18 Q And when it doesn't happen, what
19 conclusions can you draw about the efficacy?
20 DR. ELLISON: Objection. Form.
21 Foundation.
22 A When it doesn't, I don't think you can draw

1 any conclusions about the efficacy, but it raises
2 some questions in one's mind about what exactly the
3 drug is doing. Sometimes it doesn't make any
4 difference because you might not expect really to see
5 something in one kind of an outcome, whereas you
6 might want it to happen in another.
7 Q When you say "sometimes it doesn't make any
8 difference," are you referring to whether or not all
9 the outcomes point to the same effect?
10 A Yes, that's what I'm talking about.
11 Q Dr. Miller, you have worked as an
12 investigator in clinical trials for multiple
13 sclerosis, correct?
14 A Correct.
15 Q And in your experience as an investigator
16 in clinical trials for multiple sclerosis, have you
17 ever used relapse rate as an outcome measure?
18 A Yes.
19 Q As a primary outcome measure?
20 A Yes.
21 Q As a secondary outcome measure?
22 A Yes.

1 Q In your experience as an investigator in
2 clinical trials for multiple sclerosis, have you ever
3 used EDSS as an outcome measure?
4 A Yes, in some -- in some way or another.
5 Q As a primary outcome measure?
6 A Yes.
7 Q As a secondary outcome measure?
8 A Yes.
9 Can we take a five-minute break?
10 Q Can I ask --
11 A You may ask. It's not that much of an
12 emergency.
13 Q Okay. I was going to say one question, but
14 it's actually three, it's a follow-on.
15 A Go ahead.
16 Q In your experience as an investigator in
17 clinical trials for multiple sclerosis, have you ever
18 used frequency and severity of exacerbation as an
19 outcome measure?
20 A Well, frequency would really sort of turn
21 out to be the same as relapse rate, I think. At
22 least that's how I would interpret frequency. I

1 don't recall using severity of relapses as an outcome
2 measure.
3 Q Okay. Then have you used the combination
4 of frequency and severity of exacerbations as an
5 outcome measure?
6 A I don't know that I've used that.
7 DR. KAN: We can break.
8 (Recess 1:54 p.m. - 2:08 p.m.)
9 BY DR. KAN:
10 Q Dr. Miller, is it your opinion that the FDA
11 was not concerned about higher cancer risks
12 associated with Mavenclad based on the CLARITY
13 results?
14 DR. ELLISON: Objection. Form.
15 Foundation.
16 A We don't have -- we don't have an exhibit
17 of the FDA's complete response letter based on the
18 Merck press release, they didn't indicate that there
19 was a specific FDA concern about cancer risk.
20 Q Well, based on your knowledge and
21 experience as a practicing clinician in multiple
22 sclerosis, is it your opinion that the FDA was not

1 concerned about higher cancer risks associated with
2 Mavenclad based on the CLARITY results?
3 DR. ELLISON: Objection. Form.
4 Foundation.
5 A Well, I can't be sure what the FDA was --
6 was basing any of its concerns on. As I said, I
7 haven't seen their complete response letter, so the
8 only information I have to make any judgment is from
9 the prescribing information. And since the
10 prescribing information has a warning about possible
11 cancer risk, I presume the FDA had some concerns
12 about that.
13 Q But you can't presume whether or not those
14 concerns from the FDA were based on the CLARITY
15 results, correct?
16 A Well, I can't -- I can't know exactly what
17 the FDA based its labeling things on. I don't see
18 that information.
19 Q Prior to Mavenclad's approval, you were
20 aware that both American and European regulatory
21 agencies had denied approval of cladribine for the
22 treatment of multiple sclerosis, correct?

1 A Yes.
2 Q And your opinion is that prior art studies
3 demonstrated cladribine's safety in treating multiple
4 sclerosis, correct?
5 A Well, in general -- in general, I felt it
6 supported safety, but concerns were raised about the
7 possibility of cancer.
8 Q But your opinion, as set forth in your
9 declaration, is that prior art studies demonstrated
10 cladribine's safety in treating multiple sclerosis,
11 correct?
12 A Well, a POSA, as of 2004, would have had no
13 reason to doubt the safety of an oral preparation of
14 cladribine.
15 Q Do you agree that it is important to
16 consider safety issues in the choice of an initial
17 disease-modifying therapy?
18 A A choice of an initial disease-modifying
19 therapy or any disease-modifying therapy at any point
20 in time always requires an assessment of the relative
21 risks and the relative safety of -- and the relative
22 efficacy of a particular agent. So we always

1 consider those things --
2 Q So --
3 A -- at least I always consider those things.
4 Q Sorry, I did not mean to interrupt you.
5 So you would agree, then, that while
6 efficacy is very important, it must be balanced by
7 acceptable risk, correct?
8 A I would agree that efficacy must be
9 balanced by acceptable risks.
10 Q Do you agree that using cladribine as an
11 initial disease-modifying therapy carries the risk of
12 potentially very serious or even fatal adverse
13 events?
14 A Well, virtually every drug that we use
15 carries some level -- some level of risk for serious
16 or even fatal adverse events.
17 Q So with respect to cladribine, would you
18 agree, then, that using cladribine as an initial
19 disease-modifying therapy carries a risk of
20 potentially very serious or even fatal events,
21 correct?
22 A A POSA, as of 2004, should have

1 recognized -- would have recognized that there was a
2 potential risk of infections with cladribine, but
3 would also have known that the prior art had not, for
4 the most part, demonstrated a significant risk, if
5 the drug were used in -- in formulations such as that
6 of Bodor and in regimens comparable to that of
7 Stelmasiak.
8 Q Do you agree that prior to Mavenclad's
9 approval, cladribine raised safety concerns
10 particularly related to malignancies for regulators?
11 A Prior to Mavenclad's approval?
12 Q Correct.
13 A Yes, I would agree.
14 DR. KAN: Okay. I'm going to introduce
15 another exhibit and we're going to mark this as 2078.
16 And, Dave, if you could please email that
17 to Eldora.
18 (Miller Exhibit 2078 marked for
19 identification.)
20 Q Dr. Miller, do you recognize Exhibit 2078
21 that was just handed to you?
22 A Yes.

1 Q This is a published commentary that you
2 authored, correct?
3 A Yes.
4 DR. KAN: I'm sorry, before I continue, do
5 we want to wait --
6 DR. ELLISON: Did you send it?
7 MR. BASSETT: I emailed it as soon as --
8 DR. ELLISON: Did you send it to just me or
9 to --
10 MR. BASSETT: Just you.
11 DR. ELLISON: We don't need to wait --
12 DR. KAN: Okay.
13 DR. ELLISON: Thank you.
14 BY DR. KAN:
15 Q The commentary is from 2016, correct?
16 A Yes.
17 Q And the commentary is from the journal,
18 Multiple Sclerosis Journal, correct?
19 A Yes.
20 Q The title of this commentary is "Multiple
21 sclerosis should be treated using a step-down
22 strategy rather than a step-up strategy." Correct?

1 A Yes.
2 Q So the first page of Exhibit 2078 is
3 labeled 1402. And based on the title, your
4 commentary is on multiple sclerosis should be treated
5 using a step-down strategy rather than a step-up
6 strategy, correct?
7 A Yes. But before you ask me any questions,
8 I would like to read it.
9 Q Sure.
10 A Okay.
11 Q So turning to page 1402, if you look at the
12 left column, first paragraph, here you note that
13 Professor Gavin Giovannoni, G-i-o-v-a-n-n-o-n-i,
14 argues that "initiation of disease-modifying therapy
15 (DMT) for multiple sclerosis (MS) should utilize a
16 step-down approach." Correct?
17 A That's correct.
18 Q And so a step-down approach is one that
19 begins with a high-efficacy induction strategy,
20 correct?
21 A Not necessarily.
22 Q As characterized in your paper -- sorry, in

1 your commentary at 1402, left column, first
2 paragraph, you wrote, "(i.e., beginning with a
3 high-efficacy induction strategy)." And that follows
4 right after a step-down approach, correct?
5 A You read the sentence correctly. What I'm
6 -- not all high-efficacy therapies use induction
7 strategies, and I don't have the Giovannoni yes part
8 of this series of articles. Here the title of his
9 article was "Multiple sclerosis should be treated
10 using a step-down strategy rather than a step-up
11 strategy." Yes, it doesn't mention anything about
12 induction there, so that's why I'm not sure.
13 Q But in your first sentence of this
14 commentary, either you -- well, you wrote that Dr. --
15 or Professor Giovannoni argued that initiation of
16 disease-modifying therapy for multiple
17 sclerosis should utilize a step-down approach that is
18 beginning with a high-efficacy induction strategy,
19 correct?
20 A Yes. Because I presume that
21 Dr. Giovannoni, in his article, probably talked about
22 therapies that might have an induction strategy

1 rather than a continued use.
2 Q And staying on page 1402, the left column,
3 seven lines from the bottom, here you wrote, "In
4 making his argument for a step-down approach,
5 Giovannoni focuses on an induction therapy with what
6 he regards as high-efficacy DMT, including treatments
7 such as alemtuzumab" -- a-l-e-m-t-u-z-u-m-a-b --
8 "cladribine, (an agent which has heretofore been
9 denied approval by both American and European
10 regulatory agencies)." Correct?
11 A Yes.
12 Q That was a true and accurate statement when
13 you published it in 2016?
14 A That he made that argument for that? Yes,
15 that was a true statement.
16 Q Yes. And Giovannoni's argument for a
17 step-down approach included the use of alemtuzumab
18 and cladribine, correct?
19 A Yes, it did.
20 Q So as of 2016, you were aware that both
21 American and European regulatory agencies had denied
22 approval of cladribine for the treatment of multiple

1 sclerosis, correct?
2 DR. ELLISON: Objection. Scope.
3 Relevance.
4 A Yes, I was aware.
5 Q Staying on page 1402, if you look to the
6 right column, middle paragraph, here you start the
7 paragraph by stating, "In advocating for his
8 step-down approach, Giovannoni has essentially
9 borrowed the 'time is brain' concept from the stroke
10 field, albeit on a longer time spectrum." Correct?
11 A Correct.
12 Q And here you're referring to Giovannoni's
13 step-down approach, correct?
14 A Yes.
15 Q And if you look to the last paragraph of
16 page 1402, on the right column you start the
17 paragraph by stating, "Most importantly, Giovannoni
18 has neglected to consider safety issues in the choice
19 of the initial DMT." Correct?
20 A Yes.
21 Q That was a true and accurate statement when
22 you published it in 2016?

1 DR. ELLISON: Objection. Relevance.
2 A Well, I meant that at least in his
3 commentary he did not consider it.
4 Q And in his commentary, you mean
5 Giovannoni's commentary on step-down approach,
6 correct?
7 A Correct.
8 Q And in the very next sentence you wrote,
9 "While efficacy is very important, it must be
10 balanced by acceptable risk." Correct?
11 A Correct.
12 Q And that was a true and accurate statement
13 when you published it in 2016, correct?
14 A That's my -- that was my opinion in 2016 --
15 Q Is that your --
16 A Still my opinion.
17 Q Okay. In saying that efficacy "must be
18 balanced by acceptable risk," do you mean that one
19 must consider the overall benefit risk profile?
20 DR. ELLISON: Objection. Form.
21 Foundation.
22 A You have to consider the benefit, the

1 potential benefits of the drug, the potential risks
2 of the drug, and the potential benefits and risks of
3 not using the drug.
4 Q And you continue that same paragraph by
5 saying, "The high-efficacy strategies he advocates
6 carry the risk of potentially very serious or even
7 fatal adverse events." Correct?
8 A Yes.
9 Q And that was a true and accurate statement
10 when you published it in 2016, correct?
11 A Referring in that sentence to strategies.
12 Q And when you say "the high-efficacy
13 strategies he advocates," you're referring to that
14 step-down approach advocated by Giovannoni, correct?
15 A Yes.
16 Q You agree that Giovannoni's high-efficacy
17 strategies carry the risk of potentially very serious
18 or even fatal adverse events, correct?
19 A I agree.
20 Q And Giovannoni's high-efficacy strategies
21 include cladribine, correct?
22 A He did include cladribine.

1 Q In the next sentence you wrote,
2 "Alemtuzumab is associated with serious autoimmune
3 disorders; cladribine raised safety concerns,
4 particularly related to malignancies, for
5 regulators." Correct?
6 A Yes.
7 Q That was a true and accurate statement when
8 you published it in 2016, correct?
9 A Yes.
10 Q Regarding your statement with respect to
11 cladribine, specifically that cladribine raises --
12 cladribine raised safety concerns particularly
13 related to malignancies, you cite to reference 9,
14 correct?
15 A Yes.
16 Q And if you turn to page 1403 in Exhibit
17 2078, reference 9 is cited as Giovannoni --
18 A It's the CLARITY trial report.
19 Q I'm just going to read the cite into the
20 record. "Giovannoni G, Comig" -- C-o-m-i-g -- "Cook
21 S, et al., A placebo-controlled trial of oral
22 cladribine for relapsing multiple sclerosis, New

1 England Journal of Medicine, 2010; 362:416 to 426."
2 I read that correctly, correct?
3 A Yes.
4 Q And you identified that reference as the
5 CLARITY trial report. And that is the same
6 Giovannoni publication as Exhibit 2033, which you
7 considered in forming your opinions, correct?
8 A Yes.
9 Q I will hand you a copy of 2033 that has
10 previously been marked in both proceedings.
11 And Exhibit 2033, this publication by
12 Giovannoni that is also titled "A Placebo-Controlled
13 Trial of Oral Cladribine for Relapsing Remitting
14 Multiple Sclerosis" in the New England Journal of
15 Medicine from 2020, starting at page 146, discloses
16 the results of the CLARITY clinical trial, correct?
17 A Correct.
18 Q So your statement from Exhibit 2078 that
19 cladribine raised safety concerns, particularly
20 related to malignancies, for regulators, was,
21 therefore, based on the CLARITY clinical trial
22 results, correct?

1 A Yes, this was my assumption since this was
2 a key part of the evaluation by regulators.
3 Q So you agree that the FDA was concerned
4 about cancer risks associated with Mavenclad based on
5 the CLARITY results, correct?
6 DR. ELLISON: Objection. Form.
7 Foundation.
8 A Well, this was -- this was a presumption of
9 mine. I didn't have any direct information from the
10 FDA in 2016 about exactly why they did not approve --
11 did not approve the drug. But the information about
12 malignancies was present in the CLARITY trial
13 results.
14 Q So in 2016 you made the presumption that
15 the FDA was concerned about cancer risks associated
16 with Mavenclad based on the CLARITY results, correct?
17 DR. ELLISON: Objection. Form.
18 Foundation.
19 A Yes, that was my presumption.
20 Q And you told that presumption to the world
21 in your 2016 commentary, correct?
22 A No.

1 Q You disseminated that presumption to the
2 multiple sclerosis community when you published it in
3 the Multiple Sclerosis Journal in 2016, correct?
4 A I didn't publish anything about what had
5 raised their concerns in this particular article.
6 I'm telling you now that's what I presumed. I didn't
7 tell the world that.
8 Q Your -- in this publication of yours, the
9 publication included the statement that "cladribine
10 raised safety concerns, particularly related to
11 malignancies, for regulators," correct?
12 A Yes.
13 Q Okay. We can set this aside.
14 I would like to introduce what has
15 previously been marked as Exhibit 2038 in the 480 and
16 481 IPRs.
17 Dr. Miller, do you recognize Exhibit 2038
18 as the article by Fierce Biotech that you considered
19 in forming your opinions for your second declaration?
20 A Yes, I recognize it.
21 Q And you reviewed Exhibit 2038 before
22 signing your declaration, correct?

1 A Yes.
2 Q The title of the article that is marked as
3 Exhibit 2038 is "Merck Receives Complete Response
4 Letter From FDA on Cladribine Tablets New Drug
5 Application." Correct?
6 A Correct.
7 Q This is an article about the complete
8 response letter that Merck received from FDA
9 regarding Merck's new drug application for cladribine
10 tablets, correct?
11 A Correct.
12 Q If you look at the first page of Exhibit
13 2038, the second paragraph, that paragraph starts by
14 stating, "A complete response letter (CRL) is issued
15 by the FDA when the agency's review of a file is
16 complete and the application cannot be approved in
17 its present form." Correct?
18 A Yes.
19 Q And the paragraph continues with "In the"
20 -- "In the complete response letter, the FDA
21 concluded that substantial evidence of cladribine
22 tablets' effectiveness was provided by the CLARITY 1

1 study. However, the FDA has requested the company
2 provide an improved understanding of safety risks and
3 the overall benefit-risk profile either through
4 additional analyses or by additional studies."
5 Correct?
6 A Correct.
7 Q According to Exhibit 2038, FDA concluded
8 the CLARITY study provided substantial evidence of
9 cladribine tablets' effectiveness, correct?
10 A That's correct, that's what it says.
11 Q According to Exhibit 2038, despite the
12 evidence of effectiveness, FDA requested that Merck
13 provide an improved understanding of safety risks,
14 correct?
15 A Correct.
16 Q And staying on this first page of Exhibit
17 2038, please go to the third paragraph, second
18 sentence.
19 And I'm going to note that the third
20 paragraph is not well-delineated, but it states in
21 the second sentence, "'We look forward to working
22 with the FDA to address safety issues in its letter

1 and will continue to move toward identifying a
2 potential path that provides patients and physicians
3 the opportunity to have access to cladribine tablets
4 in the treatment of MS.'" Correct?
5 A Well, some of the words are cut off, but I
6 presume it's correct.
7 Q Noted.
8 According to Exhibit 2038, FDA raised
9 safety issues in the complete response letter,
10 correct?
11 A Well, they didn't raise safety issues.
12 They asked for an improved understanding of safety
13 risks. That's what this statement says. I don't
14 know what the complete response letter says.
15 Q So that paragraph we just read or that
16 sentence we just read in the third paragraph that
17 states, "'We look forward to working with the FDA to
18 address the safety issues in this letter'" suggests
19 that FDA raised safety issues, correct?
20 DR. ELLISON: Objection. Form.
21 Foundation.
22 A Yes, that sentence suggests that the CRL

1 raised safety issues.
2 Q By sending a CRL to Merck, that meant FDA
3 was unable to approve Merck's cladribine tablets,
4 correct?
5 DR. ELLISON: Objection. Form.
6 Foundation. Scope.
7 A They were unable to approve it at that
8 time.
9 Q This was because, as you noted, FDA thought
10 more information was needed about safety, correct?
11 DR. ELLISON: Objection. Form.
12 Foundation. Scope.
13 A Merck stated that the FDA has requested the
14 company provide an improved understanding of safety
15 risks and the overall benefit-risk profile.
16 Q Well, this is an article by Fierce Biotech,
17 not Merck, correct?
18 A This is an article by Fierce Biotech, yes.
19 Q And as reported by this article, the FDA
20 requested that Merck provide an improved
21 understanding of safety risks and the overall
22 benefit-risk profile, correct?

1 DR. ELLISON: Objection. Form.
2 Foundation. Scope. Hearsay.
3 A That's what Fierce Biotech said the FDA had
4 requested.
5 Q And Fierce Biotech suggested that was the
6 basis for why FDA could not approve Merck's
7 cladribine tablets at the time, correct?
8 DR. ELLISON: Objection. Foundation.
9 Scope. Hearsay.
10 A It doesn't specifically say that, no.
11 Q But it suggests that the FDA raised safety
12 concerns about cladribine, correct?
13 DR. ELLISON: Objection. Foundation.
14 Hearsay.
15 A It doesn't indicate what concerns the FDA
16 raised. It only indicates that the FDA requested
17 that Merck provide an improved understanding of
18 safety risks and the overall risk-benefit profile.
19 Q This article suggests that Merck needed to
20 address safety issues, correct?
21 A This article quotes Fereydoun Firouz,
22 president and CEO of the subsidiary -- U.S.

1 subsidiary EMD Serono, that -- that quote indicates
2 that they were working with the FDA to address safety
3 issues. Fierce Biotech doesn't say anything about
4 what the FDA said.
5 Q You agree that FDA, in evaluating the
6 CLARITY study, was evaluating administration of oral
7 cladribine according at the claimed methods, correct?
8 A No, I disagree. The Mavenclad prescribing
9 information does not adhere to the claimed methods.
10 Q In your opinion, does the prior art have to
11 express skepticism about the exact regimen in the
12 claimed -- in the challenged claims to be relevant?
13 DR. ELLISON: Objection. Foundation.
14 Scope.
15 A Could you re-ask that question, please.
16 Q In your opinion, does the prior art have to
17 express skepticism about the exact regimen in the
18 challenged claims in order to be relevant?
19 DR. ELLISON: Objection. Foundation.
20 Scope.
21 A In order for skepticism to be an indicator
22 among obviousness, it has to be in line with the full

1 scope of the claims and it has to have a connection
2 to the unique features of the claimed invention.
3 Q And when you say "the full scope of the
4 claims," you mean every single embodiment included in
5 the claims?
6 A Well, at least most the scope must be
7 appropriate.
8 Q So most embodiments, but not all?
9 A I think it must be in full scope with all
10 the claims.
11 Q What is your understanding of the term
12 "full scope"?
13 A My understanding of the terms was must --
14 must apply to the preparations, the formulations, the
15 schedule of administration, whatever is written in
16 the claims.
17 Q So I see you're looking at your
18 declaration. Is it Exhibit 1084 that you're looking
19 at, your second declaration?
20 A Yes.
21 Q Are you looking at a specific paragraph?
22 A I was looking at a number of paragraphs.

1 Q Could you turn to your declaration Exhibit
2 1084 in the 481 IPR.
3 And I've not introduced that exhibit, so
4 let me do so now. So this was Exhibit -- no, that's
5 not correct. I believe I have introduced that
6 exhibit.
7 No, I apologize for going back and forth.
8 Let me introduce Exhibit 1084, an exhibit in IPR-481,
9 unless I've already given you a copy.
10 Yeah, I think I have. Sorry for the
11 confusion.
12 DR. ELLISON: You have.
13 DR. KAN: Okay.
14 BY DR. KAN:
15 Q If you go to paragraph 43 at pages 31 to
16 32.
17 A Mm-hmm.
18 Q Okay. So this is Exhibit 1084 from the 481
19 proceeding. You state, "I understand that in order
20 to demonstrate skepticism to support a nonobviousness
21 argument, the evidence provided must, one" -- have
22 you found paragraph 43?

1 A Sorry. I think you stopped in
2 mid-sentence.
3 Q I wanted to make sure you got there.
4 A I'm there.
5 Q Okay. I'll start over.
6 At paragraph 43 you wrote, "I understand
7 that in order to demonstrate skepticism to support a
8 nonobviousness argument, the evidence provided must:
9 1, be in line with the full scope of the claims; that
10 is, the art should express skepticism for roughly the
11 full scope of the claimed invention, not just one
12 embodiment of the claimed invention, and have a
13 connection to the unique features of the claimed
14 invention." Correct?
15 A Correct.
16 Q So when you say "not just one embodiment,"
17 do you have a number of embodiments in mind in terms
18 of what full scope would be?
19 DR. ELLISON: Objection. Form.
20 Foundation.
21 A I don't have a specific number in mind.
22 Q Does it have to be all the embodiments of

1 the claimed invention?
2 A My understanding is that it would be at
3 least most of the embodiments, not necessarily the
4 full scope. Roughly the full scope.
5 Q In your opinion, the prior art would have
6 to disclose the exact claimed regimen in order to
7 express skepticism of the claimed regimen?
8 DR. ELLISON: Objection. Form.
9 Foundation.
10 A Please reread the question.
11 Q In your opinion, the prior art would have
12 to disclose the exact claimed regimen in order to
13 disclose -- strike that. Let me start over.
14 In your opinion, the prior art would have
15 to disclose the exact claimed regimen in order to
16 express skepticism of the claimed regimen?
17 DR. ELLISON: Objection. Form.
18 Foundation.
19 A I don't believe the prior art would need
20 to -- would need to specify the exact -- the exact
21 regimen, but a POSA using ordinary judgment and
22 creativity should be able to create that art.

1 Q I'm sorry. What do you mean by "should be
2 able to create that art"?
3 A Should be able to create -- create a
4 regimen very similar or identical.
5 Q So my question was in order for prior art
6 to express skepticism of the claimed regimen, would
7 the prior art have to disclose the exact claimed
8 regimen?
9 DR. ELLISON: Objection. Form.
10 Foundation.
11 A Reread your question, please.
12 Q In order for prior art to express
13 skepticism of the claimed regimen, would the prior
14 art have to disclose the exact claimed regimen?
15 DR. ELLISON: Objection. Form.
16 Foundation.
17 A The prior art would not have had to
18 disclose the exact regimen.
19 Q I would like to introduce what has
20 previously been marked as Exhibit 2060, 2-0-6-0, in
21 the 480 and 481 IPRs.
22 Dr. Miller, do you recognize Exhibit 2060

1 as the article by Fierce Pharma that you considered
2 in forming your opinions for your second declaration?
3 A I recognize it.
4 Q And you reviewed Exhibit 2060 before
5 signing your declaration, correct?
6 A Yes, I did.
7 Q The title of Exhibit 2060 is "Better 8
8 years than" -- strike that.
9 The title of the article in Exhibit 2060 is
10 "Better 8 years late than never: Merck KGaA nabs FDA
11 nod for MS drug Mavenclad." Correct?
12 A That's the title of the article.
13 Q This is an article about FDA's approval of
14 Mavenclad, correct?
15 A Yes, it is.
16 Q Please turn to the first page of Exhibit
17 2060, four paragraphs down. The first sentence
18 states, "The FDA originally slapped Mavenclad with a
19 complete response letter back in 2011, citing the
20 need for more safety and efficacy data." Correct?
21 A That's what it says.
22 Q According to Exhibit 2060, the FDA issued a

1 complete response letter for Mavenclad asking for
2 more safety and efficacy data, correct?
3 A That's what the article says. Again, I
4 haven't seen the complete response letter, so I don't
5 know if this is an accurate representation of what it
6 said.
7 Q Do you recall that Dr. Lublin cited to
8 Exhibit 2060 to support his opinion that FDA had
9 initial concerns of increased cancer risks associated
10 with Mavenclad?
11 A I do recall that Dr. Lublin mentioned that.
12 Q And specifically, he cited to Exhibit 2060
13 to support that opinion?
14 A I can't remember that.
15 Q I'll introduce what has previously been
16 marked as Exhibit 2051 in the 480 IPR.
17 Do you recognize Exhibit 2051 from the 480
18 IPR, Dr. Miller?
19 A I do.
20 Q Exhibit 2051 is the declaration of Fred D.
21 Lublin, correct?
22 A Yes.

1 Q And you reviewed Exhibit 2051 in forming
2 your opinions for your second declaration, correct?
3 A I did.
4 Q And if you turn to page 107 of Exhibit
5 2051.
6 A Page 107, yes.
7 Q At the bottom is paragraph 201, correct?
8 A Yes.
9 Q And here Dr. Lublin wrote, "FDA approved
10 Mavenclad in 2019 on the basis of the results from
11 the 96-week CLARITY trial (ClinicalTrials.gov number
12 NCT00213135) in combination with 10 years of safety
13 data that overcame FDA's initial concerns of
14 increased cancer risks associated with Mavenclad."
15 Correct?
16 A That's what Dr. Lublin wrote, yes.
17 Q And Dr. Lublin cites to Exhibit 2060 --
18 A And to 2040. I don't know whether
19 Dr. Lublin saw that 10 years of safety data were
20 submitted to the FDA because I don't -- we don't have
21 the FDA's exact statement here.
22 Q But in support of this opinion by

1 Dr. Lublin, he cites to Exhibit 2040 and 2060,
2 correct?
3 A He does.
4 Q And we were just looking at Exhibit 2060.
5 A We were.
6 Q And so Dr. Lublin's statement in paragraph
7 201 of Exhibit 2050 [sic], with respect to the higher
8 cancer risks that the FDA was concerned about is
9 supported by Exhibit 2060, correct?
10 DR. ELLISON: Objection. Form.
11 Foundation.
12 A Please restate the question.
13 Q Dr. Lublin cites to Exhibit 2060 to support
14 his opinion that FDA had initial concerns of
15 increased cancer risks associated with Mavenclad,
16 correct?
17 A Yes, he does.
18 Q And we saw in Exhibit 2060 that the FDA had
19 originally flagged concerns of higher cancer risks
20 associated with Mavenclad, correct?
21 A Can you point out where you're reading?
22 Q So Exhibit 2060 -- I was going to say four

1 paragraphs down, sorry.
2 Could we turn to page 2 of Exhibit 2060,
3 four paragraphs down, it states, "The FDA originally
4 flagged concerns of higher cancer risks associated
5 with Mavenclad, but Merck defeated the claim, thanks
6 in part to a 2015 study that ran a meta-analysis of
7 11 phase 3 trials from seven disease-modifying MS
8 drugs."
9 A Yes, I see that sentence.
10 Q So according to Exhibit 2060, the FDA
11 flagged concerns of higher cancer risks associated
12 with Mavenclad, correct?
13 DR. ELLISON: Objection. Foundation.
14 Hearsay.
15 A Yes, this is all -- I don't know whether
16 this is the interpretation of Fierce Pharma or what
17 the actual FDA said because I haven't seen what the
18 FDA said.
19 Q But at least according to Exhibit 2060,
20 this is what was reported with respect to the FDA's
21 concerns correct?
22 DR. ELLISON: Objection. Form.

1 Foundation. Hearsay.
2 A That's what the -- that's what the document
3 says, yes.
4 Q And Dr. Lublin cited to this document,
5 correct?
6 DR. ELLISON: Objection. Relevance.
7 A Dr. Lublin did cite to this reference.
8 Q So Dr. Lublin's statement that we read in
9 paragraph 201 of Exhibit 2051 from the 480 IPR was
10 accurate, correct?
11 DR. ELLISON: Objection. Foundation.
12 Form.
13 A Dr. Lublin's statement in paragraph 201 is
14 not -- is not borne out in the Fierce Pharma
15 document. You haven't cited anything in the Fierce
16 Pharma document about combination of 10 years of
17 safety data.
18 Q Dr. Lublin's statement with respect to the
19 FDA's initial concerns of increased cancer risks
20 associated with Mavenclad is supported by the Fierce
21 Pharma article, correct?
22 DR. ELLISON: Objection. Form.

1 Foundation.
2 A The Fierce Pharma data doesn't say anything
3 about 10 years of safety data.
4 Q But the Fierce Pharma article does comment
5 on the FDA's concerns of higher cancer risks
6 associated with Mavenclad, correct?
7 DR. ELLISON: Objection. Hearsay.
8 A The Fierce Pharma papers says that the FDA
9 flagged concerns of higher cancer risks associated
10 with Mavenclad.
11 Q And Dr. Lublin's opinion also indicates
12 that the FDA had initial concerns of increased cancer
13 risks associated with Mavenclad, correct?
14 A No, it doesn't say that in paragraph 201.
15 Q The last part --
16 A Yeah. Overcame the initial concerns, yes,
17 okay. So yes, he indicates that the FDA had initial
18 concerns, but he says it was overcome in combination
19 with 10 years of safety data.
20 Q Well, at least with respect to the FDA's
21 initial concerns of increased cancer risks, that is
22 supported by Exhibit 2060, correct?

1 DR. ELLISON: Objection. Foundation.
2 Hearsay.
3 A The Fierce Pharma paper said, as I've
4 repeatedly said, the FDA originally flagged concerns
5 of higher cancer risks associated with Mavenclad.
6 Q And Dr. Lublin makes a similar statement in
7 his declaration at paragraph 201, correct?
8 A Dr. Lublin says that the FDA had initial
9 concerns of increased cancer risks.
10 Q And so Dr. Lublin's statement, at least
11 with respect to the part that you just read, is
12 supported by Exhibit 2060, correct?
13 DR. ELLISON: Objection. Foundation.
14 Hearsay.
15 A The fact that there were original concerns
16 of higher cancer risks by the FDA is supported.
17 Q And if we go to the first paragraph of
18 Exhibit 2060 of this Fierce Pharma article, it also
19 states that "Up to 10 years of safety data has paid
20 off for Merck KGaA's oral multiple sclerosis
21 treatment Mavenclad." Correct?
22 A It says that.

1 Q This suggests that the 10 years of safety
2 data submitted by Merck overcame the FDA's concerns,
3 correct?
4 A Where are you reading?
5 Q I'm just asking you your opinion on what
6 the first sentence of Exhibit 2060 suggests.
7 DR. ELLISON: Objection. Foundation.
8 A Well, this whole -- this whole article is
9 an interpretation by the commentators of Fierce
10 Pharma based on their interpretations of -- of the
11 FDA approval.
12 Q And a POSA would understand this article to
13 indicate that there were 10 years of safety data that
14 paid off for Merck's oral multiple sclerosis
15 treatment drug, correct?
16 DR. ELLISON: Objection. Relevance.
17 A A POSA wouldn't have -- a POSA would not
18 have understood what data the FDA used to base its
19 approval on. This is all Fierce Pharma's
20 interpretation.
21 Q A POSA reading Fierce Pharma's
22 interpretation would understand that there was up to

1 10 years of safety data that paid off for Merck's
2 oral multiple sclerosis treatment Mavenclad, correct?
3 A A POSA would have felt that was Fierce
4 Pharma's opinion.
5 Q Okay. I'm going to introduce what has
6 previously been marked as Exhibit 2051 in the 481
7 IPR.
8 DR. ELLISON: Can we take a quick break
9 before you move on to other questions?
10 DR. KAN: Yes.
11 DR. ELLISON: Thank you.
12 (Recess 3:11 p.m. - 3:17 p.m.)
13 DR. KAN: I'm going to hold off on
14 introducing this, so don't worry about that.
15 BY DR. KAN:
16 Q Dr. Miller, in your opinion, for results of
17 the claimed method of the '947 patent to be
18 unexpected, the results must be compared to the
19 closest prior art, correct?
20 A That's my understanding.
21 Q In your opinion, the closest prior art
22 reference is Bodor, correct?

1 A Yes.
2 Q And in your opinion, for results of the
3 claimed method of the '947 patent to be unexpected,
4 the results must be compared to Bodor, correct?
5 A They must be compared to -- to the --
6 repeat the question.
7 Q In your opinion, for results of the claimed
8 method of the '947 patent to be unexpected, the
9 results must be compared to Bodor, correct?
10 A My understanding is that to be considered
11 unexpectedly superior results, they need to be
12 compared to the closest prior art. And in my
13 opinion, Bodor represents the closest prior art.
14 Q With respect to the results of the --
15 strike that.
16 With respect to the claimed method of the
17 '947 patent, correct?
18 A Yes.
19 Q In your opinion, for the results of the
20 claimed method of the '947 patent to be unexpected,
21 the inventors had to have conducted a clinical trial
22 comparing their regimen to Bodor's regimen then,

1 correct?
2 DR. ELLISON: Objection. Foundation.
3 A No, I don't believe they have to do a trial
4 comparing head-to-head against Bodor's regimen.
5 (Discussion off the record.)
6 BY DR. KAN:
7 Q In your opinion, for the results of the
8 claimed method of the '947 patent to be unexpected,
9 what results from Bodor's disclosure would the
10 results have to be compared against?
11 DR. ELLISON: Objection. Form.
12 Foundation.
13 A My understanding is that the closest prior
14 art is considered to be the one that has the most
15 elements in common with the claimed invention, and
16 Bodor meets those qualities.
17 Q And Bodor does not disclose any results for
18 that particular method that is in common with the
19 claimed invention, correct?
20 DR. ELLISON: Objection. Form.
21 Foundation.
22 A Would you please ask the question again.

1 Q Bodor does not disclose any results for the
2 method that includes these elements in common with
3 the claimed invention, correct?
4 A Bodor does not -- does not claim results.
5 Q In your opinion, for results of the claimed
6 method of the '947 patent to be unexpected, the
7 results, as compared to Bodor, must be in line with
8 the full scope of the claimed method, correct?
9 A It should be roughly in line with the full
10 scope.
11 Q In your opinion, the results of the claimed
12 method of the '947 patent could only be unexpected if
13 the inventors compared every possible oral dosage
14 form with every possible formulation in every
15 possible form of multiple sclerosis, each in a
16 clinical trial against Bodor's regimen?
17 DR. ELLISON: Objection. Form.
18 Foundation.
19 A No, I don't think I stated that.
20 Q Are you looking at Exhibit 1084, your
21 second declaration right now?
22 A I am.

1 Q And if you turn to pages 81 to 82 of
2 Exhibit 1084 from the 480 IPR, paragraph 124 spans
3 those pages, correct?
4 A Spans pages 82 to 83. You said paragraph
5 124, right?
6 Q Correct, of Exhibit 1084 of the 480
7 proceeding.
8 A Oh, I'm sorry. I'm looking at the --
9 Q That's fine.
10 A What was the page again?
11 Q 81 to 82. And paragraph 124 spans 81 to
12 82, correct?
13 A Yes.
14 Q So at paragraph 124, three sentences in, so
15 I would say that's the top of page 82, you wrote,
16 "However, the CLARITY clinical trials only
17 administered one oral cladribine dosage form
18 (tablets) and only one formulation of that dosage
19 form to patients with only one type of multiple
20 sclerosis: RRMS." Correct?
21 A That's correct.
22 Q You continue by stating, "Dr. Lublin

1 provides no evidence that other types of oral
2 cladribine formulations (e.g., solutions, capsules,
3 mucoadhesive tablets) would have provided
4 unexpectedly superior results." Correct?
5 A Yes.
6 Q So is it your opinion that for the results
7 to be unexpected, the results would have to show that
8 every possible oral dosage form with every possible
9 cladribine formulation was effective in every
10 possible form of multiple sclerosis?
11 A No, that's not my opinion.
12 Q In order for the results to be unexpected,
13 would the results have to show that every possible
14 oral dosage form has unexpected results?
15 A I wouldn't expect that they would have to
16 show that every possible dosage form would have
17 unexpected results. But I would expect that they'd
18 have to show that more than one dosage form or more
19 than one formulation of the dosage form in more than
20 one form of MS would have to be satisfied.
21 Q So in your opinion, for the results of the
22 claimed method of the '903 patent to be unexpected,

1 the results must also be compared to the closest
2 prior art, correct?
3 A Say that again, please.
4 Q In your opinion, for results of the claimed
5 method of the '903 patent to be unexpected, the
6 results must be compared to the closest prior art,
7 correct?
8 A That's my understanding of what
9 unexpectedly superior results would require.
10 Q And in your opinion, the closest prior art
11 reference for the '903 patent claims is also Bodor,
12 correct?
13 A Yes.
14 Q And in your opinion, for results of the
15 claimed method of the '903 patent to be unexpected,
16 the results must be compared to Bodor, correct?
17 A No, that's not my opinion.
18 Q You agree that for the results of the
19 claimed method of the '903 patent to be unexpected,
20 the results must be compared to the closest prior
21 art, correct?
22 A The results must be compared to -- must be

1 compared to the closest prior art, but the closest
2 prior art need not necessarily have conducted those
3 experiments.
4 Q But for the results of the '903 patent to
5 be unexpected, the results had to be compared to
6 Bodor, correct?
7 DR. ELLISON: Objection. Form.
8 Foundation.
9 A Yes, they have to be compared to the
10 closest prior art, which is Bodor.
11 Q And in your opinion, for results of the
12 claimed method of the '903 patent to be unexpected,
13 the results, as compared to Bodor, must be in line
14 with the full scope of the claimed method in the '903
15 patent, correct?
16 DR. ELLISON: Objection. Form.
17 A With roughly the full scope of the claim.
18 Q In your opinion, the results of the claimed
19 method of the '903 patent could only be unexpected if
20 the inventors compared every possible oral dosage
21 form with every possible formulation to patients with
22 RRMS and early secondary progressive multiple

1 sclerosis?
2 A That's not my opinion.
3 Q In your opinion, for the results of the
4 claimed method of the '903 patent to be unexpected,
5 the results must show at least more than one dosage
6 form, correct?
7 A I would expect they would either need to
8 use more than one dosage form or compare it in more
9 than one form of multiple sclerosis or more than one
10 formulation of the dosage form.
11 Q In your opinion, a POSA would have
12 understood that Bodor discloses a safe, effective,
13 and convenient oral therapy for multiple sclerosis,
14 correct?
15 A Yes.
16 Q Your opinion -- in your opinion, a POSA
17 would have understood that Stelmasiak discloses a
18 safe, effective, and convenient oral therapy for
19 multiple sclerosis, correct?
20 A Well, a POSA would have understood that
21 combining Bodor and Stelmasiak that produces a --
22 discloses a safe, effective, and convenient oral

1 therapy for MS.
2 Q So in your opinion, Stelmasiak alone --
3 strike that.
4 In your opinion, a POSA would not have
5 understood Stelmasiak alone to disclose a safe,
6 effective, and convenient oral therapy for MS?
7 DR. ELLISON: Objection. Foundation.
8 A Well, Stelmasiak is not the closest prior
9 art, and my understanding is that a POSA is allowed
10 to combine the art to form -- to form a useful method
11 of treatment in this case, and combination of Bodor
12 and Stelmasiak produces a safe, effective, and
13 convenient oral therapy for MS.
14 Q So the combination of Bodor and Stelmasiak
15 produces a safe and effective, convenient oral
16 therapy for MS, correct?
17 A Yes.
18 Q In your opinion, would a POSA have
19 understood Bodor alone to disclose a safe, effective,
20 and convenient oral therapy for MS?
21 A Yes.
22 Q In your opinion, would a POSA have

1 understood Stelmasiak alone to disclose a safe,
2 effective, and convenient oral therapy for MS?
3 DR. ELLISON: Objection. Foundation.
4 A Yes.
5 Q In your opinion, Bodor alone would have
6 satisfied any long-felt need for a safe, effective,
7 and convenient oral therapy for MS, correct?
8 A Well, my understanding of the requirements
9 for a satisfying a long-felt unmet need must -- means
10 that there's a technical problem that needs to be
11 solved. In my opinion, the only technical problem
12 that would have needed to be solved here was an
13 oral -- was an oral -- satisfactory oral treatment
14 which Bodor certainly -- certainly met.
15 Q So to the extent there was a long-felt
16 unmet need for a safe, effective, and convenient oral
17 therapy for MS, is it your opinion that Bodor would
18 have satisfied that need?
19 A It is my opinion that Bodor would have
20 satisfied that need.
21 Q Is it your opinion that Bodor alone would
22 have satisfied that long-felt unmet need for a safe,

1 convenient oral therapy for MS?
2 A I think -- I think Bodor alone would have
3 met that, yes.
4 Q And would Stelmasiak alone have satisfied
5 any long-felt need for a safe, effective, and
6 convenient oral therapy for MS?
7 DR. ELLISON: Objection. Form.
8 Foundation.
9 A In my opinion, yes.
10 Q Earlier we were talking about Copaxone,
11 otherwise known as glatiramer acetate, being used to
12 treat MS patients, correct?
13 A We were talking about that, yes.
14 Q And that dosing regimen that's FDA approved
15 was 20 milligrams per day, correct?
16 A I think the reference date you gave was
17 2004, that was correct then.
18 Q And in your opinion, the patient dose with
19 Copaxone at 20 milligrams per day, would they be
20 considered to be -- strike that.
21 In your opinion, MS patients being treated
22 with glatiramer acetate at 20 milligrams a day would

1 be dosed continuously, correct?
2 DR. ELLISON: Objection. Form.
3 Foundation.
4 A "Continuously" is a funny word, so people
5 are going to use that term differently. Glatiramer
6 was given every day.
7 Q Would you agree, then, that there was no
8 extended glatiramer acetate-free period during the
9 dosing regimen for glatiramer acetate?
10 DR. ELLISON: Objection. Foundation.
11 A I would agree that there was not an
12 extended treatment-free period.
13 Q Would you consider treatment with
14 glatiramer acetate to require continued
15 administration?
16 DR. ELLISON: Objection. Foundation.
17 A What do you mean by "continued
18 administration"?
19 Q Do you have an understanding of the term
20 "continued administration"?
21 A Yes, but continued has a -- to me, needs a
22 time frame.

1 Q What time frame --
2 A Two days, two weeks, two months, two years,
3 two decades.
4 Q If a treatment is continued for two weeks,
5 that would be considered a continued administration?
6 A For two weeks?
7 Q And the same would be true for two years,
8 correct?
9 DR. ELLISON: Objection. Form.
10 Foundation.
11 A I would say then it was continued for two
12 years. It's continued for whatever period you're
13 taking it.
14 Q Are there any disease-modifying treatments
15 that you're aware of that do not require continued
16 administration?
17 A Yes.
18 Q And what would those be?
19 A What do you mean by "continued
20 administration"?
21 Q Well, you agreed that there are
22 disease-modifying treatments that do not require

1 continued administration. So what would those
2 disease-modifying treatments be?
3 A Well, I would certainly consider Ocrevus to
4 not require continued administration.
5 Q And how is that --
6 A In the sense that it's not given -- not
7 given every day.
8 I would consider -- I would consider
9 Briumvi certainly not to be continued administration.
10 I would consider mitoxantrone not to be continued
11 administration. One could consider potentially
12 natalizumab, which is given once a month, as not to
13 require continued administration, at least on a
14 daily -- on a daily basis. I would consider
15 Kesimpta, again, usually after the beginning is given
16 once a month, you could consider that not to be
17 considered administration. It depends on the time
18 frame.
19 I would consider alemtuzumab not to be
20 required continued administration.
21 Q Let's just take natalizumab, for example.
22 N-a-t-a-l-i-z-u-m-a-b. It's not given every day, but

1 you don't cease administration at any point in time
2 based on the recommended dosage, correct?
3 DR. ELLISON: Objection. Form.
4 Foundation.
5 A Well, as a matter -- as a matter of routine
6 course, you would not discontinue the medication at
7 any particular point.
8 Q So if we use that to -- strike that.
9 For mitoxantrone, based on the recommended
10 dosage, administration actually is ceased at some
11 point, correct?
12 A It was ceased at some point.
13 Q And for Briumvi, is administration ceased
14 at any point in time based on the recommended dosage?
15 A Not at the current -- not at the current
16 moment.
17 Q And what about Ocrevus?
18 A It's currently not -- it's currently not
19 discontinued, although studies are under way to see
20 if it may be discontinued.
21 In a lot of these circumstances we don't
22 know if the drug's going to be discontinued because

1 it hasn't been studied.
2 Q And staying on our discussion -- our
3 initial discussion leading into this on glatiramer
4 acetate and the Copaxone label, if you could pull
5 that up one more time, that's Exhibit 2017.
6 A I got it.
7 Q If you -- I'll wait until counsel has it as
8 well.
9 DR. ELLISON: I'm good.
10 Q If you turn to page 6 of Exhibit 2017, we
11 had been looking at this Table 2 titled "Study 2
12 Efficacy Results," do you remember?
13 A Yes, I certainly remember.
14 Q And you had referenced the P values in the
15 rightmost column. You had indicated that some showed
16 statistical significance but others did not, correct?
17 A Correct.
18 Q In your experience, have you worked with
19 confidence intervals as an example of statistical
20 significance?
21 A I have.
22 Q So if this study had reported confidence

1 intervals for results for the glatiramer acetate
2 group and placebo group instead of P values, and
3 those two confidence intervals overlapped, would that
4 tell you anything about the statistical significance
5 of those results?
6 A If what two confidence intervals overlapped
7 what?
8 Q So if we look at the first -- I guess the
9 second row corresponding to mean number of relapses,
10 we see that glatiramer acetate patients had a mean
11 number of 1.19 relapses per year and the placebo
12 group had a mean number of 1.68 relapses per year --
13 for two years, sorry.
14 A Yeah, you're referring to row 1?
15 Q Yes.
16 A Yes.
17 Q So if instead of reporting P values, that
18 the 1.19 and the 1.68 was reported with 95 percent
19 confidence intervals instead, and those confidence
20 intervals for row 1 for each of the two groups
21 overlapped, would that tell us anything about the
22 statistical significance of the results?

1 DR. ELLISON: Objection. Form.
2 Foundation. Relevance.
3 A The two confidence intervals overlapped
4 what?
5 Q With each other.
6 DR. ELLISON: Objection. Form.
7 Foundation. Relevance.
8 A So if the confidence intervals encompassed
9 one, that would tell us that it was not -- it was not
10 a significant difference. I don't know how to get
11 from a P value to a confidence interval.
12 Q But a confidence interval does tell you
13 about statistical significance?
14 A That's one way of looking for statistical
15 significance.
16 Q And you stated that if the confidence
17 intervals encompassed one, that would tell you that
18 it was not statistically significant. Is that
19 correct?
20 A That's my understanding.
21 Q Okay. I'm just going to set forth some
22 numbers so I can try and understand that statement

1 you just made.
2 So let's say the 1.19 mean number relapses
3 over two years for the glatiramer acetate group had a
4 confidence interval -- a 95 percent confidence
5 interval of, let's say, 0.8 to 1.5, and for the
6 placebo group the confidence interval was 1.3 to 1.9,
7 you would agree that those two confidence intervals
8 overlap, correct?
9 DR. ELLISON: Objection. Form.
10 Foundation. Scope. Relevance.
11 A I think the confidence interval has to
12 relate to the difference between the two arms that
13 you're studying.
14 Q You mean the 1.19 to the 1.68?
15 A Yes.
16 Q So could you clarify your earlier statement
17 that if one confidence interval encompasses one, what
18 you mean by that?
19 A I can't explain exactly from a statistical
20 point of view this confidence intervals. But the
21 confidence intervals have to be above or beyond and
22 not spanning a value that doesn't allow you to,

1 confidently understand that there's a difference.
2 Q When you say above and beyond, what do you
3 mean by that?
4 A Well, you could have -- you could have the
5 difference clearly being in a positive direction or
6 clearly being in a negative direction. If it expands
7 -- expands -- crosses that line, then you don't have
8 confidence that the result is not happening by chance
9 alone.
10 Q So if two confidence intervals overlap, for
11 instance, the confidence level -- I'll start over.
12 If two confidence intervals overlap, for
13 example, the confidence interval for the glatiramer
14 acetate group and the confidence interval for the
15 placebo group for row 1 corresponding to mean number
16 of relapses, does that overlap in confidence interval
17 tell you anything about the statistical significance
18 of the results?
19 DR. ELLISON: Objection. Foundation.
20 Scope. Relevance.
21 A If the confidence intervals overlapped, I
22 would not believe that they were -- that there was a

1 statistically meaningful result.
2 DR. KAN: We would just like to take a
3 five-minute break.
4 DR. ELLISON: Sure. No problem.
5 (Recess 3:51 p.m. - 4:00 p.m.)
6 BY DR. KAN:
7 Q Dr. Miller, during our breaks today did you
8 talk to counsel about the substance of your
9 deposition at all?
10 A No.
11 DR. KAN: We have no further questions at
12 this time.
13 DR. ELLISON: Okay. Why don't we go off
14 the record.
15 (Recess 4:00 p.m. - 4:02 p.m.)
16 EXAMINATION
17 BY DR. ELLISON:
18 Q Dr. Miller, I have a question for you.
19 Today you have been presented with various
20 exhibits, including exhibits relating to cladribine's
21 safety. To what extent, if any, do the exhibits
22 discussed today impact your opinions as set forth in

1 your first and second declarations in these cases?
2 A I stand by the opinions in my declarations;
3 they are not modified by the exhibits presented
4 today.
5 DR. ELLISON: Thank you. I have no further
6 questions.
7 DR. KAN: Okay. We have no further
8 questions.
9 Thank you, Dr. Miller.
10 DR. ELLISON: Thank you, Dr. Miller.
11 (Time noted: 4:03 p.m.)
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13 *****
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1 CERTIFICATE OF CERTIFIED SHORTHAND REPORTER
2 NOTARY PUBLIC
3 I, MONIQUE VOUTHOURIS, Certified Court Reporter
4 and Notary Public within and for the State of New
5 York, do hereby certify:
6 That AARON E. MILLER, M.D., the witness whose
7 deposition is hereinbefore set forth, was duly sworn
8 by me before the commencement of such deposition, and
9 that such deposition was taken before me and is a
10 true record of the testimony given by such witness.
11 I further certify that the adverse party,
12 HOPEWELL PHARMA VENTURES, INC., was represented by
13 counsel at the deposition.
14 I further certify that the deposition of AARON
15 E. MILLER, M.D., occurred at NEW YORK HILTON MIDTOWN,
16 1335 6th Avenue, New York, New York, on Monday, May
17 13, 2024, commencing at 8:59 a.m. to 4:03 p.m.
18 I further certify that I am not related to any
19 of the parties to this action by blood or marriage, I
20 am not employed by or an attorney to any of the
21 parties to this action, and that I am in no way
22 interested, financially or otherwise, in the outcome

of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 14th day of May 2024.

Monique Vouthouris

_____

Monique Vouthouris, CCR, RPR, CRR
Notary Public of the State of New York
My commission expires: December 1, 2027

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