

1 UNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD
3
4 MYLAN PHARMACEUTICALS INC.,
5 Petitioner,
6 v.
7 ALLERGAN, INC.,
8 Patent Owner.
9 _____/

10
11 Case IPR2016-01127
12 Patent 8,685,930
13 Case IPR2016-01128
14 Patent 8,629,111
15 Case IPR2016-01129
16 Patent 8,642,556
17 Case IPR2016-01130
18 Patent 8,633,162
19 Case IPR2016-01131
20 Patent 8,648,048
21 Case IPR2016-01132
22 Patent 9,248,191
23

24 DEPOSITION OF ANDREW F. CALMAN, M.D., PH.D.
25 WEDNESDAY, JULY 12, 2017

Page 2

1

REPORTED BY: MEGAN F. ALVAREZ, RPR, CSR 12470

2

JOB LA-133836

3

4

5

--o0o--

6

7

8

BE IT REMEMBERED that, pursuant to Notice, and

9

on Wednesday, JULY 12, 2017, commencing at WILSON

10

SONSINI GOODRICH & ROSATI, One Market Street, Spear

11

Tower, Suite 3300, San Francisco, California, before me,

12

Megan F. Alvarez, a Certified Shorthand Reporter,

13

Registered Professional Reporter, personally appeared

14

for their deposition

15

ANDREW F. CALMAN, M.D., PH.D.

16

17

called as a witness by Patent Owner, who, having been

18

first duly sworn, was examined and testified as follows:

19

--o0o--

20

21

22

23

24

25

Page 3

1

I N D E X

2

INDEX OF EXAMINATIONS

3

EXAMINATION BY MR. KANE7

4

EXAMINATION BY MR. MILLS159

5

EXAMINATION BY MR. KANE168

6

EXAMINATION BY MR. MILLS169

7

8

--o0o--

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Page 4

1

EXHIBITS MARKED FOR IDENTIFICATION

2

No. Description Page

3

Exhibit 2077 Local Cyclosporine Therapy133

4

for Experimental Autoimmune

5

Uveitis in Rats, Nussenblatt,

6

et al., Pages 1559 through

7

1562, Ophthalmology Archives

8

9

--o0o--

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Page 5

1

EXHIBITS PREVIOUSLY MARKED FOR IDENTIFICATION

2

REFERRED TO IN THIS DEPOSITION

3

4

Exhibit No. Page Line

5

4216 16

6

100749 25

7

1011127 11

8

103913 25

9

1058125 13

10

200849 7

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

| | |
|--|--|
| <p style="text-align: right;">Page 6</p> <p>1 A P P E A R A N C E S</p> <p>2 APPEARANCES:</p> <p>3</p> <p>4 FOR THE PATENT OWNER:</p> <p>5 MICHAEL J. KANE, ESQ.</p> <p>6 TASHA M. FRANCIS, PH.D., ESQ.</p> <p>7 FISH & RICHARDSON P.C.</p> <p>8 3200 RBC PLAZA</p> <p>9 60 SOUTH SIXTH STREET</p> <p>10 MINNEAPOLIS, MINNESOTA 55402</p> <p>11 612.335.5070</p> <p>12 KANE@FR.COM</p> <p>13 TFRANCIS@FR.COM</p> <p>14</p> <p>15 FOR THE REMAINING PETITIONERS:</p> <p>16 (APPEARING TELEPHONICALLY)</p> <p>17 GARY SPEIER, ESQ.</p> <p>18 CARLSON, CASPERS, VANDENBURGH, LINDQUIST</p> <p>19 & SCHUMAN, P.A.</p> <p>20 225 SOUTH SIXTH STREET, SUITE 4200</p> <p>21 MINNEAPOLIS, MN 55402</p> <p>22 GSPEIER@CARLSONCASPERS.COM</p> <p>23</p> <p>24 FOR THE RESPONDENT:</p> <p>25 JAD A. MILLS, ESQ.</p> <p>ANNA PHILLIPS, ESQ.</p> <p>WILSON SONSINI GOODRICH & ROSATI</p> <p>701 FIFTH AVENUE, SUITE 5100</p> <p>SEATTLE, WASHINGTON 98104</p> <p>206.883.2554</p> <p>JMILLS@WSGR.COM</p> <p style="text-align: center;">--oOo--</p> | <p style="text-align: right;">Page 8</p> <p>1 that she can get our both of our comments down. I'm</p> <p>2 a fast talker as well, so we'll both have to try to</p> <p>3 watch that a little bit and not try to step on each</p> <p>4 other. Okay?</p> <p>5 A. Yes.</p> <p>6 Q. If I ask you a question that you don't</p> <p>7 understand, please let me know and I'll to do a</p> <p>8 better job on that. Okay?</p> <p>9 A. Okay.</p> <p>10 Q. It's also important that since we are</p> <p>11 trying to create a transcript here that you need to</p> <p>12 answer verbally. Yeses, nos, not nods of the head</p> <p>13 or shaking of the head or the uh-huhs or huh-uhs,</p> <p>14 that kind of thing. All right?</p> <p>15 A. Yes.</p> <p>16 Q. We'll try to take a break approximately on</p> <p>17 an hourly basis or so. But if you need a break</p> <p>18 somewhere in the middle, let us know. We can do</p> <p>19 that. We just won't -- we'll just ask if there's an</p> <p>20 outstanding question, that you answer the question</p> <p>21 before we take a break. All right?</p> <p>22 A. Yes.</p> <p>23 Q. Of the 18 times you've been deposed, how</p> <p>24 many of those related to patent issues?</p> <p>25 A. Two, to the best of my recollection.</p> |
| <p style="text-align: right;">Page 7</p> <p>1 WEDNESDAY, JULY 12, 2017, 9:08 A.M.</p> <p>2</p> <p>3 ANDREW F. CALMAN, M.D., PH.D.,</p> <p>4 having been first duly sworn, was examined and</p> <p>5 testified as follows:</p> <p>6</p> <p>7 EXAMINATION</p> <p>8 BY MR. KANE:</p> <p>9 Q. Good morning. Could you state your name</p> <p>10 for the record?</p> <p>11 A. Andrew Frederick Calman.</p> <p>12 Q. And what's your current business address,</p> <p>13 Dr. Calman?</p> <p>14 A. 2480 Mission Street, San Francisco,</p> <p>15 California 94110.</p> <p>16 Q. And I believe you've been deposed before,</p> <p>17 right?</p> <p>18 A. Yes.</p> <p>19 Q. How many times?</p> <p>20 A. About 18.</p> <p>21 Q. Okay. So you know the general ground</p> <p>22 rules, then. But before we get started, I'm going</p> <p>23 to ask you a series of questions, you're going to</p> <p>24 provide the answers. It will be important to let me</p> <p>25 finish my question before you start your answer so</p> | <p style="text-align: right;">Page 9</p> <p>1 Q. And can you describe generally what those</p> <p>2 depositions were?</p> <p>3 A. Well, there was one in the Markman case,</p> <p>4 and I believe there's just one -- in the Markman</p> <p>5 phase of Allergan v. Teva Mylan, et al., for this</p> <p>6 product. And there was one or two, but I believe</p> <p>7 it's just one, on the invalidity and noninfringement</p> <p>8 phase of that same case.</p> <p>9 Q. So both of your depositions that related</p> <p>10 to patents were in connection with the district</p> <p>11 court litigation over Restasis currently pending in</p> <p>12 Texas?</p> <p>13 A. Correct.</p> <p>14 Q. Okay.</p> <p>15 A. There was another matter, but it was an</p> <p>16 antitrust matter that had grown out of a patent</p> <p>17 matter. But I was not involved in the patent phase</p> <p>18 at all.</p> <p>19 Q. Okay. And then, in general, in the other</p> <p>20 16 or so depositions that you've given, what did</p> <p>21 they generally relate to?</p> <p>22 A. Injuries and medical malpractice.</p> <p>23 Q. Okay.</p> <p>24 A. With a smattering of other things. There</p> <p>25 was an employment discrimination case.</p> |

| | |
|--|--|
| <p style="text-align: right;">Page 10</p> <p>1 I think that's it.</p> <p>2 Q. Okay.</p> <p>3 A. Off the top of my head.</p> <p>4 Q. The other --</p> <p>5 A. Oh, there was a wrongful death case.</p> <p>6 Q. Okay. The other matter that related --</p> <p>7 the antitrust matter that you mentioned, did that</p> <p>8 relate to a drug?</p> <p>9 A. Yes.</p> <p>10 Q. What kind of drug was that?</p> <p>11 A. An antibiotic eye drop.</p> <p>12 Q. Who were the parties?</p> <p>13 A. Apotex and Allergan.</p> <p>14 Q. And who did you represent in that case?</p> <p>15 A. Well, I was engaged by Allergan -- excuse</p> <p>16 me -- by Apotex.</p> <p>17 Q. Where was that case located, if you</p> <p>18 recall?</p> <p>19 A. I think Delaware. But it never went to</p> <p>20 trial, so I don't know for sure.</p> <p>21 Q. What was the name of the product?</p> <p>22 A. Zymaxid.</p> <p>23 Q. Do you recall the time frame when that</p> <p>24 occurred?</p> <p>25 A. It settled earlier this year.</p> | <p style="text-align: right;">Page 12</p> <p>1 the -- to my knowledge, is part of the U.S. Patent</p> <p>2 and Trademark Office.</p> <p>3 Q. Okay. And you understand you're</p> <p>4 testifying under oath today?</p> <p>5 A. Of course.</p> <p>6 Q. So the testimony today is just as though</p> <p>7 you were in a courtroom giving it in front of a</p> <p>8 judge or jury.</p> <p>9 A. Of course.</p> <p>10 Q. Okay. Any reason you can't give accurate</p> <p>11 or truthful, complete testimony today?</p> <p>12 A. No.</p> <p>13 Q. What did you do to prepare for the</p> <p>14 deposition today?</p> <p>15 A. I reviewed various documents. I met with</p> <p>16 counsel, reviewed -- you know, obviously reviewed my</p> <p>17 declaration and others and prior art.</p> <p>18 Q. When did you meet with counsel?</p> <p>19 A. Yesterday and the day before.</p> <p>20 Q. How long?</p> <p>21 A. About eight hours each day.</p> <p>22 Q. Okay. And who -- who was present at those</p> <p>23 meetings?</p> <p>24 A. Jad Mills. Anna Phillips. I think</p> <p>25 Wendy Devine may have poked her head in for a brief</p> |
| <p style="text-align: right;">Page 11</p> <p>1 Q. Okay. And generally --</p> <p>2 A. You know what? I don't think I was</p> <p>3 deposed for that case, though. I didn't actually</p> <p>4 testify.</p> <p>5 Q. Did you provide a report?</p> <p>6 A. Yeah.</p> <p>7 Q. And, again, just at a high level, what did</p> <p>8 the report relate to?</p> <p>9 A. Well, it's subject to a protective order</p> <p>10 which I believe is still in effect. So what I think</p> <p>11 I can probably safely share is what I've seen in</p> <p>12 public press releases, that it was -- not my term</p> <p>13 but press term -- was a product switching case</p> <p>14 related to this drug.</p> <p>15 Q. Okay. You understand that this deposition</p> <p>16 relates to several -- what are called IPRs pending</p> <p>17 in the patent office?</p> <p>18 A. That's my understanding.</p> <p>19 Q. And what do you understand an IPR to be?</p> <p>20 A. Well, my understanding of inter partes</p> <p>21 review is it's a pathway where parties can challenge</p> <p>22 the validity of patents through -- rather than going</p> <p>23 through the court system, going through what's</p> <p>24 called the PTAB, which I believe stands for Patent</p> <p>25 and Trademark Appeals Board, which is a part of</p> | <p style="text-align: right;">Page 13</p> <p>1 period.</p> <p>2 Q. Anyone else?</p> <p>3 A. Not that I recall.</p> <p>4 Q. Anybody on the phone?</p> <p>5 A. Not that I'm aware of.</p> <p>6 Q. Okay. Do you recall what documents you</p> <p>7 reviewed?</p> <p>8 A. Well, I'm sure I can't remember every</p> <p>9 single thing. But, in general, I reviewed the</p> <p>10 various declarations in the case, the various -- not</p> <p>11 court, but the various PTAB documents such as</p> <p>12 institution, petition, response, order, and then the</p> <p>13 various prior art references.</p> <p>14 Q. Okay. Okay. Did you talk to anyone other</p> <p>15 than counsel in preparation for your deposition?</p> <p>16 A. No.</p> <p>17 Q. Did you talk to anyone at Mylan in</p> <p>18 preparation for the deposition?</p> <p>19 A. No.</p> <p>20 Q. Have you ever spoken to anyone at Mylan</p> <p>21 about this case?</p> <p>22 A. Not to the best of my recollection.</p> <p>23 Q. Okay. All right. We have -- handing you</p> <p>24 what's been marked previously as Exhibit 1039.</p> <p>25 And do you recognize this document,</p> |

| | |
|--|--|
| <p style="text-align: right;">Page 14</p> <p>1 Dr. Calman?</p> <p>2 A. Yes.</p> <p>3 Q. What is this?</p> <p>4 A. This is my declaration for the six IPR</p> <p>5 cases.</p> <p>6 Q. Okay. And if you turn to page 55, that's</p> <p>7 your electronic signature?</p> <p>8 A. Yes.</p> <p>9 Q. And it's dated June 30th, 2017?</p> <p>10 A. Yes.</p> <p>11 Q. And you understand this same declaration</p> <p>12 was filed in all six of the IPR proceedings?</p> <p>13 A. That is my understanding.</p> <p>14 Q. Okay. When did you begin working on the</p> <p>15 declaration for the IPRs?</p> <p>16 A. It would have been late May or early June,</p> <p>17 to the best of my recollection.</p> <p>18 Q. Okay. Do you recall approximately how</p> <p>19 much time you spent drafting the declaration?</p> <p>20 A. I don't have a precise idea of that. I</p> <p>21 can give you an estimate. It's probably somewhere</p> <p>22 between 20 and 30 hours.</p> <p>23 Q. Okay. Did you draft the declaration</p> <p>24 yourself?</p> <p>25 A. Well, it was a -- it was a collaboration</p> | <p style="text-align: right;">Page 16</p> <p>1 The drafting process generally included</p> <p>2 sending drafts back and forth and changing them.</p> <p>3 BY MR. KANE:</p> <p>4 Q. And did you -- did you originate the first</p> <p>5 draft that was exchanged back and forth, or did</p> <p>6 counsel do the drafting?</p> <p>7 A. I think there were parts of both. Parts</p> <p>8 of it were initially written by me, and parts were</p> <p>9 initially written by counsel, if I recall correctly.</p> <p>10 I don't -- there were a lot of drafts. I don't have</p> <p>11 a precise recollection.</p> <p>12 Q. Okay. Let's take a quick look and hand</p> <p>13 you another exhibit here, Dr. Calman.</p> <p>14 Handing you what's been marked previously</p> <p>15 as Exhibit 42.</p> <p>16 Do you recognize this?</p> <p>17 A. I do.</p> <p>18 Q. What is this?</p> <p>19 A. This is my CV.</p> <p>20 Q. And is this dated June 29, 2017?</p> <p>21 A. Yes.</p> <p>22 Q. Was it accurate as of that date?</p> <p>23 A. Yes.</p> <p>24 Q. Have there been any changes?</p> <p>25 A. Let me look.</p> |
| <p style="text-align: right;">Page 15</p> <p>1 with counsel.</p> <p>2 Q. And which counsel collaborated?</p> <p>3 A. WSGR.</p> <p>4 Q. Anyone else?</p> <p>5 A. No, not unless -- not that I'm aware of.</p> <p>6 Q. And which counsel at Wilson?</p> <p>7 A. I'm sorry?</p> <p>8 Q. Which counsel at Wilson Sonsini?</p> <p>9 A. Let's see. Jad Mills. Grace Winschel,</p> <p>10 W-I-N-S-C-H-E-L. Anna Phillips. Wendy Devine. I</p> <p>11 think Jacqueline Altman may have been involved.</p> <p>12 And there may have been others involved,</p> <p>13 but those are the ones that I'm aware of.</p> <p>14 Q. And can you describe the drafting process</p> <p>15 generally?</p> <p>16 MR. MILLS: And I'm -- at this point, I'm</p> <p>17 just going to issue an instruction that, on the</p> <p>18 basis of work product and privilege, you should</p> <p>19 disclose in answering the questions posed to you</p> <p>20 today your opinions as well as the bases for your</p> <p>21 opinions, but you should not disclose the contents</p> <p>22 of any confidential communications you may have had</p> <p>23 with counsel.</p> <p>24 THE WITNESS: So let me look at the</p> <p>25 question again.</p> | <p style="text-align: right;">Page 17</p> <p>1 Not to the best of my knowledge.</p> <p>2 Q. And --</p> <p>3 A. Actually, there's one change. Let me look</p> <p>4 at this. And I have changed this on my subsequent</p> <p>5 versions.</p> <p>6 There are two hospitals here where I no</p> <p>7 longer practice in the list of admitting privileges,</p> <p>8 and those are San Francisco General Hospital and</p> <p>9 St. Mary's Hospital.</p> <p>10 Q. Okay. Thank you for that update.</p> <p>11 And when you say "practice," you are a</p> <p>12 practicing ophthalmologist, right?</p> <p>13 A. Correct.</p> <p>14 Q. And in preparing your analysis, you relied</p> <p>15 on lawyers for the legal principles that you were to</p> <p>16 incorporate?</p> <p>17 A. In part.</p> <p>18 Q. And where else did you obtain information</p> <p>19 about the legal principles you were to use?</p> <p>20 A. I have done some background reading over</p> <p>21 the last couple of years.</p> <p>22 Q. In what -- can you explain what kind of</p> <p>23 background reading you've done?</p> <p>24 A. I actually enrolled in a course called</p> <p>25 OmniPrep Patent Course, which I didn't complete, but</p> |

| | |
|---|---|
| <p style="text-align: right;">Page 18</p> <p>1 I did enroll in it and went through some of their 2 materials. 3 I went to two continuing legal education 4 courses over the last two years on Hatch-Waxman. 5 And I read a book called -- it's called 6 "The Generic Challenge." 7 And I've read various articles online 8 about various patents' issues. 9 Q. Okay. In forming your opinions, you 10 relied on that additional outside reading? 11 A. Well, I would say that that was background 12 information. 13 Q. Okay. In forming your opinions, did you 14 follow any guidance that the lawyers provided in 15 terms of the legal principles that you were to 16 apply? 17 A. I would say that's a fair statement. 18 Q. I understand that you're not a lawyer; is 19 that correct? 20 A. That is correct. 21 Q. What caused you to be interested in the 22 subject of patents over the last couple of years? 23 A. I saw -- I thought it was very 24 interesting. I had some exposure to patents. My 25 brother holds 55 patents in the technology field and</p> | <p style="text-align: right;">Page 20</p> <p>1 have the ability to read and understand and apply, 2 to some degree, statistical principles. That does 3 not mean that I hold myself out to be an expert in 4 statistics per se. 5 Q. Okay. Are you offering opinions in these 6 matters as a expert in statistics? 7 A. Well, again, I think that there's some 8 semantics here. I think my prior answer is 9 applicable to your question. I do have an ability 10 to read and understand statistical data. I did not 11 perform my own statistical analysis. 12 Q. And we'll come to that. 13 You talked to Dr. Bloch, I understand? 14 MR. MILLS: Objection. Foundation. 15 THE WITNESS: Not in connection with this 16 case. 17 BY MR. KANE: 18 Q. Okay. You reviewed Dr. Bloch's 19 declaration in connection with this case? 20 A. I did. 21 Q. Okay. Do you consider yourself an expert 22 in pharmacokinetics? 23 A. Again, through my knowledge, skills, 24 training, education in 27-plus years -- more if you 25 count my lab career working in labs on various</p> |
| <p style="text-align: right;">Page 19</p> <p>1 has been an expert witness in high-tech patent 2 cases. 3 I had an invention a few years ago which I 4 thought about patenting and elected not to. 5 So that was my exposure, and my brother 6 encouraged me to explore this. And I started 7 reading about Hatch-Waxman. Some people may think 8 it's dry; I actually found it kind of interesting. 9 So I saw it as a natural outgrowth of my expert 10 witness work on smaller cases. 11 Q. When you say "smaller cases," what are you 12 referring to? 13 A. Mostly ocular injuries and medical 14 malpractice. 15 Q. I see. 16 You don't consider yourself an expert in 17 patent law? 18 A. I don't consider myself an expert in any 19 form of law. 20 Q. You don't consider yourself an expert in 21 statistics, do you? 22 A. Well, what I would say is that there are 23 degrees of expertise. And through my knowledge, 24 skills, experience, training, and education as a 25 scientist and as a clinician over many years, I do</p> | <p style="text-align: right;">Page 21</p> <p>1 projects, reviewing scientific and clinical 2 publications, working on clinical trials, and 3 serving as an expert on various cases, and, you 4 know, taking various courses, including, you know, 5 courses on evidence-based medicine and epidemiology, 6 I have acquired some expertise in understanding and 7 interpreting pharmacokinetic studies. 8 That said, I do not hold myself out an 9 expert in pharmacokinetics per se. 10 Q. Do you still work at Premier Eyecare in 11 San Francisco? 12 A. I do. 13 Q. And you're also an associate clinical 14 professor? 15 A. Yes. 16 Q. Have you taken any additional roles 17 besides those that are not listed in your CV? 18 A. Not to my knowledge. 19 Q. Okay. 20 A. "Roles" is a pretty broad category, but I 21 think I've listed the relevant professional roles 22 that I've had. 23 Q. Okay. If we look at the list of 24 publications that starts on page 8 of 25 Exhibit 1042...</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 22</p> <p>1 A. Yeah.</p> <p>2 Q. To the best of your knowledge, is that a</p> <p>3 complete list of your publications?</p> <p>4 A. Yes.</p> <p>5 Q. Do any of these publications relate to</p> <p>6 dry eye?</p> <p>7 A. No. Well, not directly anyway.</p> <p>8 Q. Okay. Have you published in any papers on</p> <p>9 KCS?</p> <p>10 A. No.</p> <p>11 Q. Have you published any papers on making</p> <p>12 ophthalmic formulations?</p> <p>13 A. Not to the best of my recollection, no.</p> <p>14 Q. And I guess on that front, do you consider</p> <p>15 yourself to be an expert in making ophthalmic</p> <p>16 formulations?</p> <p>17 A. Again, I've had 27 years in labs -- well,</p> <p>18 27 years in clinical work plus 12 years in labs</p> <p>19 doing basic research. And through that knowledge,</p> <p>20 education, skills, training, and experience, I have</p> <p>21 acquired certain knowledge about pharmaceutical</p> <p>22 formulations, including ophthalmic formulations and</p> <p>23 their application in clinical practice, in clinical</p> <p>24 trials, et cetera.</p> <p>25 So although I do have -- I have acquired</p> | <p style="text-align: right;">Page 24</p> <p>1 A. No, with the caveat that I did -- I was</p> <p>2 working with professors as a resident in</p> <p>3 ophthalmology, and we certainly used ophthalmic</p> <p>4 cyclosporin formulations at that time. Whether any</p> <p>5 of them published anything on any of the patients</p> <p>6 that I collaborated with them on, I don't know. So</p> <p>7 not to the best of my knowledge.</p> <p>8 Q. What were the nature of those formulations</p> <p>9 that you were working on?</p> <p>10 A. To the best of my recollection -- again,</p> <p>11 this was a long time ago -- we were using 2 percent</p> <p>12 cyclosporin in olive oil.</p> <p>13 Q. And was it a commercial product?</p> <p>14 A. It was a compounded product.</p> <p>15 Q. What do you mean when you say "compounded</p> <p>16 product"?</p> <p>17 A. So you go through what's called a</p> <p>18 compounding pharmacy -- in this case, it was the</p> <p>19 UCSF pharmacy -- and the pharmacist makes up the</p> <p>20 drug custom for you.</p> <p>21 Q. Okay. And this is during the time you</p> <p>22 were a resident?</p> <p>23 A. Yes.</p> <p>24 Q. And --</p> <p>25 A. And possibly part of the time I was a</p> |
| <p style="text-align: right;">Page 23</p> <p>1 some expertise in that area, I don't hold myself out</p> <p>2 to be an expert in formulation per se.</p> <p>3 Q. Okay. You mentioned you thought about</p> <p>4 filing a patent application a couple years ago.</p> <p>5 Have you ever filed a patent application?</p> <p>6 A. No.</p> <p>7 Q. In connection with that potential</p> <p>8 invention a couple years ago, did you talk to a</p> <p>9 patent lawyer?</p> <p>10 A. I don't remember if I actually talked to a</p> <p>11 patent lawyer. And it was more than a couple; it</p> <p>12 was about 12 years ago.</p> <p>13 Q. Okay. I assume that means there was never</p> <p>14 an application drafted?</p> <p>15 A. That's correct.</p> <p>16 Q. And, again, just generally, what was the</p> <p>17 nature of the potential invention?</p> <p>18 A. It was a surgical instrument.</p> <p>19 Q. For ophthalmic surgery?</p> <p>20 A. Yes.</p> <p>21 Q. So that -- do I understand correctly,</p> <p>22 then, you've never applied for a patent?</p> <p>23 A. That is correct.</p> <p>24 Q. Have you ever been involved in developing</p> <p>25 a cyclosporin ophthalmic product?</p> | <p style="text-align: right;">Page 25</p> <p>1 medical student as well.</p> <p>2 Q. Okay. And what were you using that</p> <p>3 compounded product on patients for?</p> <p>4 A. Well, we used it for sure on some patients</p> <p>5 who had had corneal transplants, and we used it on a</p> <p>6 rare condition called ligneous, L-I-G-N-E-O-U-S,</p> <p>7 conjunctivitis.</p> <p>8 You know, It's been a long time. I don't</p> <p>9 remember whether we used it on other conditions as</p> <p>10 well. I just don't remember.</p> <p>11 Q. Okay. And did you have any involvement in</p> <p>12 deciding what the formulation would be made by the</p> <p>13 compounding pharmacy?</p> <p>14 A. Well, there may have been some</p> <p>15 discussions, but I don't remember specifically.</p> <p>16 Q. Have you ever been involved in any other</p> <p>17 development of a cyclosporine ophthalmic</p> <p>18 formulation?</p> <p>19 A. Not to the best of my recollection.</p> <p>20 Q. Have you been involved in the development</p> <p>21 of any ophthalmic formulation?</p> <p>22 A. I guess it depends what you mean by</p> <p>23 "development." I've been involved certainly in</p> <p>24 clinical trials.</p> <p>25 Q. Do you recall which clinical trials?</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 26</p> <p>1 A. Well, I believe they're listed in my CV.</p> <p>2 Page 11 --</p> <p>3 Q. Okay.</p> <p>4 A. -- and 12.</p> <p>5 Q. All right. And that's a complete list?</p> <p>6 A. Well, to the best of my recollection and</p> <p>7 knowledge, yes.</p> <p>8 Q. And in these clinical trials, did you have</p> <p>9 any input into the formulations that would be used</p> <p>10 in the trials?</p> <p>11 A. Not to the best of my recollection. But I</p> <p>12 should add that there were some additional</p> <p>13 discussions with personnel in the research</p> <p>14 department at Alcon over some clinical trials of</p> <p>15 glaucoma drugs where I would have had input into</p> <p>16 which formulations were used. However, we never got</p> <p>17 past the initial discussion.</p> <p>18 Q. In that sort of a discussion, though, are</p> <p>19 you talking about the specific, say, excipients and</p> <p>20 other ingredients, or are you just talking about</p> <p>21 choosing between formulations that have been</p> <p>22 developed already?</p> <p>23 A. Definitely the second part. Potentially</p> <p>24 the first part. We didn't get to that stage --</p> <p>25 Q. Okay.</p> | <p style="text-align: right;">Page 28</p> <p>1 focus of their research.</p> <p>2 Q. Okay. In the Brimonidine formulations,</p> <p>3 did you have any input into what could be used in</p> <p>4 place of the BAK?</p> <p>5 A. No. I believe that was -- that was at an</p> <p>6 earlier stage than my involvement.</p> <p>7 Q. Okay. All right. And likewise in the</p> <p>8 Travatan, did you have any input into which</p> <p>9 preservative would be used in place of the BAK?</p> <p>10 A. Well, I know I was certainly involved in</p> <p>11 discussions. I don't remember if they were at --</p> <p>12 you know, certainly at the stage where they were</p> <p>13 disclosing the treatment protocols and rationale and</p> <p>14 basic science to the clinical investigators.</p> <p>15 Whether I was involved in discussions earlier than</p> <p>16 that, I don't have a recollection.</p> <p>17 Q. All right. Have you ever performed</p> <p>18 bioavailability analysis for the delivery of ocular</p> <p>19 drugs in animals?</p> <p>20 A. Not that I can recall.</p> <p>21 Q. Okay. Do you use Restasis in your</p> <p>22 practice?</p> <p>23 A. I do.</p> <p>24 Q. And how do you use Restasis in your</p> <p>25 practice?</p> |
| <p style="text-align: right;">Page 27</p> <p>1 A. -- in the discussions.</p> <p>2 Q. Were there any other projects you were</p> <p>3 involved in where you were having detailed</p> <p>4 discussions about excipients and other components in</p> <p>5 ophthalmic formulations in development stages?</p> <p>6 A. Well, again, it depends what stages you're</p> <p>7 talking about. The Travatan, or travoprost, studies</p> <p>8 were in part an effort to minimize toxicity to the</p> <p>9 ocular surface. And so the excipients were an</p> <p>10 important issue in those clinical trials. I was</p> <p>11 definitely involved in Phase 3 and Phase 4. I don't</p> <p>12 think I was involved in Phase 1 or Phase 2 or</p> <p>13 preclinical.</p> <p>14 Q. And in those trials, what was the</p> <p>15 excipient of concern?</p> <p>16 A. Well, the goal was to eliminate BAK. And</p> <p>17 so they were using a novel -- a novel preservative</p> <p>18 which the name is escaping me at this point. But</p> <p>19 that was the goal.</p> <p>20 Q. Okay. All right.</p> <p>21 A. And there were similar considerations. I</p> <p>22 don't know if they applied to the ones that I was</p> <p>23 directly involved with, but some of the Brimonidine</p> <p>24 formulations were also formulated -- reformulated in</p> <p>25 such a way as to eliminate BAK. And that was a</p> | <p style="text-align: right;">Page 29</p> <p>1 A. Well, as I discussed in my declaration, I</p> <p>2 individualize treatment. Some individuals with some</p> <p>3 types of dry eye and some clinical pictures, I</p> <p>4 employ it as one treatment modality.</p> <p>5 Q. Can you explain what you mean by that?</p> <p>6 A. Well, it's a -- it would be a rather</p> <p>7 lengthy discussion. But I think to summarize, I</p> <p>8 typically use it in patients with moderate to severe</p> <p>9 aqueous-deficient dry eye where I believe there is</p> <p>10 an inflammatory component as one component of their</p> <p>11 treatment plan.</p> <p>12 Q. Okay. And you understand that Restasis</p> <p>13 has been indicated to increase tear production in</p> <p>14 certain patients?</p> <p>15 A. Well, it's a very specific labeled</p> <p>16 indication. To paraphrase without having the label</p> <p>17 in front of me, it's indicated to increase tear</p> <p>18 production in patients whose tear production is</p> <p>19 presumed to be suppressed by inflammation associated</p> <p>20 with KCS.</p> <p>21 Q. And are you using it consistent with that</p> <p>22 labeling?</p> <p>23 A. To some extent, yes, but I do</p> <p>24 individualize treatment, and I don't necessarily</p> <p>25 perform before and after measurement of</p> |

| | |
|--|--|
| <p style="text-align: right;">Page 30</p> <p>1 tear production.</p> <p>2 Q. Okay. If we look back at the clinical</p> <p>3 trials you've been involved in, you mentioned</p> <p>4 Brimonidine as an example. And isn't it -- is it</p> <p>5 true that many of these studies involve</p> <p>6 glaucoma-related drugs?</p> <p>7 A. That is true.</p> <p>8 Q. Did any of them involve cyclosporin?</p> <p>9 A. I don't believe so.</p> <p>10 Q. Did any of them involve treatments for</p> <p>11 dry eye patients?</p> <p>12 A. In a sense because the -- again, the</p> <p>13 thrust of eliminating the BAK was to facilitate</p> <p>14 treatment of patients with ocular surface</p> <p>15 conditions, including that broad constellation of</p> <p>16 entities collectively known as dry eye, to be able</p> <p>17 to treat those patients for their glaucoma without</p> <p>18 comprising their ocular surface.</p> <p>19 And so that was a major focus of the</p> <p>20 Brimonidine and travoprost development. And</p> <p>21 probably was -- I mean, this was a long time ago; I</p> <p>22 don't remember the exact study protocols. But it</p> <p>23 probably was reflected in the -- in the patients --</p> <p>24 in the target patient population and the monitoring</p> <p>25 modalities.</p> | <p style="text-align: right;">Page 32</p> <p>1 list. These are some of the documents that I relied</p> <p>2 upon, yes.</p> <p>3 Q. Okay. What other documents did you rely</p> <p>4 upon?</p> <p>5 A. Well, just off the top of my head, I'm not</p> <p>6 seeing, for example, the petition, response,</p> <p>7 institution decision. I'm looking for the various</p> <p>8 declarations.</p> <p>9 So I did review petitions, responses,</p> <p>10 preliminary responses, institution decisions. I</p> <p>11 think there were a couple of orders. And then the</p> <p>12 declarations of Dr. Sheppard; Loftsson,</p> <p>13 L-O-F-T-S-S-O-N; Amiji, A-M-I-J-I; and Bloch,</p> <p>14 B-L-O-C-H.</p> <p>15 Again, off the top of my head, that's --</p> <p>16 that's what I remember reviewing. And I believe</p> <p>17 that everything that is referenced in here is listed</p> <p>18 the appendix. If not, then the reference would be</p> <p>19 in the text.</p> <p>20 Q. Okay. And so was this listing an attempt</p> <p>21 to call out the specific documents referenced in</p> <p>22 your opinion?</p> <p>23 A. I think that would be the overall thrust</p> <p>24 of it, yes.</p> <p>25 Q. Were there any documents that you</p> |
| <p style="text-align: right;">Page 31</p> <p>1 Q. If I understand correctly, the active</p> <p>2 ingredient in the treatment was being offered for</p> <p>3 glaucoma, but the concern or the issue with BAK was</p> <p>4 not to aggravate patients that were also suffering</p> <p>5 with some sort of a dry eye condition?</p> <p>6 A. That's close. I wouldn't say it exactly</p> <p>7 that way. But, yes, many of the patients who have</p> <p>8 glaucoma are also elderly. And there is a strong</p> <p>9 overlap in the target population between dry eye and</p> <p>10 glaucoma, and so that was underlying this effort.</p> <p>11 Q. But the focus was the treating the</p> <p>12 glaucoma?</p> <p>13 A. Well, these are glaucoma drugs, obviously.</p> <p>14 But at least in some cases -- and I -- I would have</p> <p>15 to go read these study protocols from 15, 20 years</p> <p>16 ago -- was towards protecting the ocular surface</p> <p>17 while treating the glaucoma.</p> <p>18 Q. Turn back to your declaration, Dr. Calman.</p> <p>19 And if we turn to appendix at page 56,</p> <p>20 please. This is entitled "List of Exhibits."</p> <p>21 Do you see that?</p> <p>22 A. I do.</p> <p>23 Q. And is this the documents that you relied</p> <p>24 upon in forming your opinions in these matters?</p> <p>25 A. Well, it's not meant to be an exhaustive</p> | <p style="text-align: right;">Page 33</p> <p>1 recall -- well, let me strike that.</p> <p>2 If you start, other than Dr. Amiji -- as</p> <p>3 you 1001 of the patents at issue, so those are six</p> <p>4 patents that are subject to the IPRs, I assume?</p> <p>5 A. Yes.</p> <p>6 Q. And 1002 is the declaration of Dr. Amiji</p> <p>7 as filed in the IPRs?</p> <p>8 A. There were six different ones, and I read</p> <p>9 one in detail and skimmed the others looking for,</p> <p>10 you know, areas that were different.</p> <p>11 Q. All right. 1004 is the file history for</p> <p>12 the '930 patent in this list.</p> <p>13 Is that a file history that you reviewed?</p> <p>14 A. Well, I reviewed all of the six file</p> <p>15 histories about a year and a half ago. And I</p> <p>16 reviewed a few relevant sections of the '930 file</p> <p>17 history for the -- in preparation for this.</p> <p>18 So, yes, I have reviewed the entire file</p> <p>19 history.</p> <p>20 Q. Okay. You have an syllabus, a file</p> <p>21 history for a U.S. patent application.</p> <p>22 Do you see that?</p> <p>23 A. That's right.</p> <p>24 Q. That's also something that you reviewed?</p> <p>25 A. Well, again, I skimmed it and I read some</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 34</p> <p>1 relevant portions, some in more detail.</p> <p>2 Q. Okay. Starting at 1006 -- strike that.</p> <p>3 Again, are there other technical documents</p> <p>4 that you relied upon in forming your opinions that</p> <p>5 are not listed in the appendix?</p> <p>6 A. Well, I'm looking. Again, you know, there</p> <p>7 are a lot of documents here, and I've reviewed a lot</p> <p>8 of documents.</p> <p>9 What I would say is that there are</p> <p>10 certainly other documents that I may have glanced at</p> <p>11 but that I did not incorporate explicitly into the</p> <p>12 declaration but that I reviewed over the years or</p> <p>13 been exposed to during my training and practice</p> <p>14 and/or during the earlier parts of the district</p> <p>15 court case.</p> <p>16 But that anything that substantively, you</p> <p>17 know, I'm quoting and relying upon directly should</p> <p>18 be referenced and/or listed in this -- in this list.</p> <p>19 But, again, as I said at the outset, this is not</p> <p>20 meant to be exhaustive.</p> <p>21 Q. How did you come into possession of the</p> <p>22 documents that are on this list?</p> <p>23 A. Most of them I encountered through the</p> <p>24 district court proceeding. Some of them I found</p> <p>25 during my literature searches.</p> | <p style="text-align: right;">Page 36</p> <p>1 BY MR. KANE:</p> <p>2 Q. Okay. You didn't feel that those were</p> <p>3 necessary to form your opinions in this case?</p> <p>4 A. It was more that I was not sure whether</p> <p>5 they would have been available to a POSA as a</p> <p>6 priority date.</p> <p>7 Q. Did you talk to Dr. Amiji in forming your</p> <p>8 opinions in this case?</p> <p>9 A. No.</p> <p>10 Q. Did you talk to Dr. Bloch in forming any</p> <p>11 opinions in connection with this case?</p> <p>12 A. No.</p> <p>13 Q. Did you talk to --</p> <p>14 A. Well, I should say Dr. Bloch and I had a</p> <p>15 conversation a few months ago in conjunction with</p> <p>16 the district court case. There may have been some</p> <p>17 overlap in materials, but they were different cases.</p> <p>18 Q. Okay.</p> <p>19 A. I have not had any discussions with</p> <p>20 Dr. Bloch with regard to the IPR case.</p> <p>21 Q. Okay. Have you ever had a discussion with</p> <p>22 Dr. Amiji?</p> <p>23 A. Not to the best of my recollection.</p> <p>24 Q. Have you had any discussions with</p> <p>25 Mr. Hoffman?</p> |
| <p style="text-align: right;">Page 35</p> <p>1 Some of them, I believe, came to my</p> <p>2 attention through the various other declarations in</p> <p>3 the case. That's -- you know, that's what I recall.</p> <p>4 Q. Did you request or look for any documents</p> <p>5 that you weren't able to obtain?</p> <p>6 A. Yes.</p> <p>7 Q. What documents were those?</p> <p>8 A. The Restasis NDA.</p> <p>9 Q. Okay. Anything else?</p> <p>10 A. Not that I recall off the top of my head.</p> <p>11 Q. Okay. Did you look at any of the FDA</p> <p>12 documents or filings related to the Restasis?</p> <p>13 MR. MILLS: Objection. Form.</p> <p>14 THE WITNESS: Not in conjunction with this</p> <p>15 case.</p> <p>16 BY MR. KANE:</p> <p>17 Q. Okay.</p> <p>18 A. Which is to say the IPR case.</p> <p>19 Q. Understood. Thank you.</p> <p>20 Did you look at any public FDA filings</p> <p>21 with respect to Restasis?</p> <p>22 MR. MILLS: Objection. Form.</p> <p>23 THE WITNESS: Well, that's what I thought</p> <p>24 you were talking about. Not in conjunction with the</p> <p>25 IPR case.</p> | <p style="text-align: right;">Page 37</p> <p>1 A. I think I may have had a discussion with</p> <p>2 him during the district court case, but I'm not</p> <p>3 sure.</p> <p>4 Q. Before you -- before filing the</p> <p>5 declarations that you filed in the IPR, did you</p> <p>6 review the declaration of Dr. Amiji filed in the</p> <p>7 IPR?</p> <p>8 MR. MILLS: Objection. Form.</p> <p>9 THE WITNESS: Yes. Well, the</p> <p>10 declarations, yes, plural.</p> <p>11 BY MR. KANE:</p> <p>12 Q. Okay. And before filing your declarations</p> <p>13 in the IPR, did you review the declarations of</p> <p>14 Dr. Bloch?</p> <p>15 MR. MILLS: Objection. Form.</p> <p>16 THE WITNESS: Yes. Or a version thereof,</p> <p>17 yes.</p> <p>18 BY MR. KANE:</p> <p>19 Q. Okay. Before filing your declarations in</p> <p>20 the IPRs, did you review the declarations of</p> <p>21 Mr. Hoffman?</p> <p>22 A. I don't believe so.</p> <p>23 Q. In reviewing the matters related to the</p> <p>24 IPR petitions, did you review the petitions filed by</p> <p>25 Apotex?</p> |

| | |
|---|---|
| <p style="text-align: right;">Page 38</p> <p>1 A. I don't think I've seen those documents.</p> <p>2 Q. Did you review any petitions filed by</p> <p>3 Akorn?</p> <p>4 A. You know, I'm trying to remember whether</p> <p>5 the petitions had other applicants besides -- or</p> <p>6 other petitioners besides Mylan on that front sheet.</p> <p>7 I don't remember.</p> <p>8 So if I did, it would have been only</p> <p>9 because they were on the same -- you know, they were</p> <p>10 cosignatories to the same petition as Mylan.</p> <p>11 Q. You don't recall reviewing any petitions</p> <p>12 other than petitions where Mylan was a party?</p> <p>13 A. That's correct.</p> <p>14 Q. Okay. You don't recall filing a --</p> <p>15 reviewing a petition by Famy Care?</p> <p>16 A. That's correct.</p> <p>17 Q. And you don't recall reviewing a petition</p> <p>18 by Teva?</p> <p>19 A. We're talking about the IPR here. That is</p> <p>20 correct.</p> <p>21 Q. You don't recall reviewing a petition by</p> <p>22 Argentum?</p> <p>23 A. No, I don't.</p> <p>24 Q. And you obviously mentioned you're aware</p> <p>25 that there are district court cases ongoing and you</p> | <p style="text-align: right;">Page 40</p> <p>1 I'm sorry.</p> <p>2 You see that a section with the heading</p> <p>3 "Claim Construction"?</p> <p>4 A. I do.</p> <p>5 Q. And in paragraph 10 there, you describe</p> <p>6 that you've been advised that the PTAB has construed</p> <p>7 the claims of the patents in suit in a particular</p> <p>8 way.</p> <p>9 Do you see that?</p> <p>10 A. I do.</p> <p>11 Q. And you say that that -- that PTAB's</p> <p>12 construction encompasses both palliative and</p> <p>13 curative treatments of the various dry eye</p> <p>14 conditions?</p> <p>15 A. To give you a precise answer, I'd prefer</p> <p>16 to have the actual institution decisions in front of</p> <p>17 me.</p> <p>18 But off the top of my head, to the best of</p> <p>19 my recollection, this is what they said.</p> <p>20 Q. Okay. And -- and this is what you used in</p> <p>21 forming your opinions?</p> <p>22 A. Correct.</p> <p>23 Q. Okay. In forming your opinions, you have</p> <p>24 relied upon the PTAB's construction as the term --</p> <p>25 in terms of the patent is encompassing treatments</p> |
| <p style="text-align: right;">Page 39</p> <p>1 filed declarations in connection with that, correct?</p> <p>2 A. I think they were reports, but yes.</p> <p>3 Q. But you've stated a couple times that</p> <p>4 those are separate cases and you view the opinions</p> <p>5 here as being separate from the opinions that you</p> <p>6 may be offering in the district court case?</p> <p>7 A. Well, I guess it depends what you mean by</p> <p>8 "separate." There are obviously different rules and</p> <p>9 different legal standards and different bodies of</p> <p>10 knowledge that can be considered in those two</p> <p>11 venues. So I have done my best to consider each one</p> <p>12 as a separate matter.</p> <p>13 Q. Okay. And you've done -- you've tried to</p> <p>14 segregate the information that might be involved in</p> <p>15 one matter versus the other and use the information</p> <p>16 for the appropriate matter?</p> <p>17 A. I probably used it in a -- say it in a</p> <p>18 slightly different way. But my intent was to</p> <p>19 basically follow the rules for each of the two</p> <p>20 matters in terms of what information could be used</p> <p>21 and what could not.</p> <p>22 Q. Okay. If we turn to paragraph 10 of</p> <p>23 Exhibit 1039, please.</p> <p>24 A. I'm sorry. Which exhibit is that one now?</p> <p>25 Q. Your report, 1039 -- or your declaration.</p> | <p style="text-align: right;">Page 41</p> <p>1 that are both palliative and curative in nature?</p> <p>2 A. I have used the PTAB's construction in</p> <p>3 that manner.</p> <p>4 Q. And you say at the bottom of the paragraph</p> <p>5 11: "Any remedy that provides relief to the</p> <p>6 patient's dry eye/KCS symptoms would be considered</p> <p>7 by the patient as well as by the prescribing</p> <p>8 physician to demonstrate therapeutic efficacy."</p> <p>9 Do you see that?</p> <p>10 A. I do see that.</p> <p>11 Q. And how does that relate, then, to the</p> <p>12 PTAB's construction regarding palliative and</p> <p>13 curative treatments?</p> <p>14 A. That's a broad question. And I think</p> <p>15 there's been a lot of confusion in this between the</p> <p>16 various parties as to what these terms mean.</p> <p>17 But applying -- in my mind, "curative"</p> <p>18 means that you give a treatment and that the</p> <p>19 condition is cured, i.e., it's gone, it's done, it's</p> <p>20 finished. It doesn't come back, which obviously</p> <p>21 does not apply to, frankly, any of these topical</p> <p>22 treatments. It may apply to some surgical</p> <p>23 treatments, for example, or in some of the other</p> <p>24 examples that I've given in the declaration.</p> <p>25 What I was trying to say in the last</p> |

| | |
|--|--|
| <p style="text-align: right;">Page 42</p> <p>1 sentence of 11 is that patient's concept of what's</p> <p>2 therapeutically effective and a doctor -- practicing</p> <p>3 clinician's concept of what's therapeutically</p> <p>4 effective is something that makes the patient feel</p> <p>5 better, patient's symptoms improve.</p> <p>6 Q. Okay. And so that would include remedies</p> <p>7 that do not increase tear production, right?</p> <p>8 A. Yes.</p> <p>9 Q. Now, Dr. Calman, you mentioned in your</p> <p>10 declaration that there are, I guess, at least two</p> <p>11 types of tears that patients form: Basal tears and</p> <p>12 reflexive tears.</p> <p>13 Do you recall that?</p> <p>14 A. I think it's an oversimplification, but</p> <p>15 it's one that we use.</p> <p>16 Q. Basal tears are produced by the lacrimal</p> <p>17 gland?</p> <p>18 A. No, that's not right.</p> <p>19 Q. Where are basal tears produced?</p> <p>20 A. They're produced in the various lacrimal</p> <p>21 glands, plural.</p> <p>22 Q. Okay.</p> <p>23 A. Which includes the main lacrimal gland and</p> <p>24 the accessory lacrimal glands.</p> <p>25 Q. And reflexive tears are also produced in</p> | <p style="text-align: right;">Page 44</p> <p>1 stimuli. And there are also emotional tears which</p> <p>2 some people consider a form of reflex tears and</p> <p>3 others consider to be a separate category.</p> <p>4 Q. All right.</p> <p>5 MR. KANE: It's been about an hour. Take</p> <p>6 a short break?</p> <p>7 THE WITNESS: Sure.</p> <p>8 (Off the record at 9:57 a.m. and back on</p> <p>9 the record at 10:10 a.m.)</p> <p>10 BY MR. KANE:</p> <p>11 Q. Now, Dr. Calman, in your practice, have</p> <p>12 you used the Schirmer tear test?</p> <p>13 A. Yes.</p> <p>14 Q. And you've used that to quantify</p> <p>15 tear production?</p> <p>16 A. It's a rough clinical test that is proxy</p> <p>17 for tear production.</p> <p>18 Q. And it provides a quantitative measurement</p> <p>19 of tear production?</p> <p>20 A. Well, it's quantitative in the sense that</p> <p>21 it gives a number and has some limitations, some of</p> <p>22 which were discussed in my declaration.</p> <p>23 Q. Okay. And that -- that test can be done</p> <p>24 with or without anesthesia?</p> <p>25 A. Yes. There's actually at least three ways</p> |
| <p style="text-align: right;">Page 43</p> <p>1 the lacrimal glands?</p> <p>2 A. Reflexive tears are produced in the</p> <p>3 lacrimal glands. And the extent to which they're</p> <p>4 produced by different types of lacrimal glands is an</p> <p>5 area that is not fully known.</p> <p>6 Q. Okay. And reflexive tears are produced in</p> <p>7 response to an irritant to the eye?</p> <p>8 A. Typically, yes.</p> <p>9 Q. And basal tears are not typically produced</p> <p>10 in response to an irritant?</p> <p>11 A. That's a pretty good -- yeah, that's a</p> <p>12 pretty close approximation, yes.</p> <p>13 Q. Okay.</p> <p>14 A. I -- to be very precise, I think -- you</p> <p>15 know, to be more precise, basal tears are still</p> <p>16 produced in the presence of an irritant as well.</p> <p>17 They're produced both in the presence and absence of</p> <p>18 an irritant.</p> <p>19 Q. Okay.</p> <p>20 A. And they may -- you know, basal, it's</p> <p>21 just -- it may vary by time of day and many other</p> <p>22 factors, so it's not like it's some concrete thing.</p> <p>23 Q. But reflexive tears are produced only in</p> <p>24 response to an irritant?</p> <p>25 A. Well, generally in response to noxious</p> | <p style="text-align: right;">Page 45</p> <p>1 to do it, yes.</p> <p>2 Q. What are the three ways to do it?</p> <p>3 A. Without anesthesia, with a topical</p> <p>4 anesthesia drop in the eye, or with nasal</p> <p>5 stimulation.</p> <p>6 Q. Okay. And is it true that Schirmer -- a</p> <p>7 Schirmer test without anesthesia measures both basal</p> <p>8 and reflexive tears?</p> <p>9 A. Well, you know, all of these are somewhat</p> <p>10 oversimplifications. But to a first approximation,</p> <p>11 I think most clinicians would agree with that</p> <p>12 statement.</p> <p>13 Q. If you perform that Schirmer test without</p> <p>14 anesthesia, is there any way to distinguish between</p> <p>15 the amount of basal tears being produced as opposed</p> <p>16 to the amount of reflexive tears being produced?</p> <p>17 A. Generally by subtracting the Schirmer</p> <p>18 without anesthesia with all the caveats and</p> <p>19 limitations of that test.</p> <p>20 Q. Okay. But running the Schirmer test</p> <p>21 without anesthesia alone, you can't distinguish</p> <p>22 between the amount of the basal tears produced and</p> <p>23 reflexive tears produced?</p> <p>24 A. Pretty much what you're getting is the</p> <p>25 total of those two.</p> |

| | |
|--|---|
| <p style="text-align: right;">Page 46</p> <p>1 Q. So as you said, then, to determine the --</p> <p>2 or strike that.</p> <p>3 In order to distinguish between the amount</p> <p>4 of basal tears and reflexive tears, you would run a</p> <p>5 Schirmer with anesthesia?</p> <p>6 A. Well, to a first approximation and within</p> <p>7 the limitations and problems within all these --</p> <p>8 problems with and limitations of all these tests,</p> <p>9 yes.</p> <p>10 It says "limitation," but it's</p> <p>11 limitations.</p> <p>12 Q. And, in fact, at paragraph -- if you want</p> <p>13 to look at paragraph 37 of your declaration,</p> <p>14 Dr. Calman.</p> <p>15 A. Yes.</p> <p>16 Q. The second sentence says: "However, the</p> <p>17 STT" -- and that stands for Schirmer tear test?</p> <p>18 A. Correct.</p> <p>19 Q. -- "with anesthesia, which is thought to</p> <p>20 measure the basal aqueous tear secretion."</p> <p>21 You see that?</p> <p>22 A. Yes.</p> <p>23 Q. So that's consistent with what you</p> <p>24 discussed, that the Schirmer tear with anesthesia is</p> <p>25 thought to measure the basal aqueous</p> | <p style="text-align: right;">Page 48</p> <p>1 Q. And you understand that Restasis was the</p> <p>2 first drug approved by the FDA to increase</p> <p>3 tear production?</p> <p>4 MR. MILLS: Objection. Form.</p> <p>5 THE WITNESS: Well, I think that depends,</p> <p>6 again, semantically on what you mean by that. It's</p> <p>7 the first prescription drug that says on the label</p> <p>8 that it increases tear production, to the best of my</p> <p>9 knowledge.</p> <p>10 BY MR. KANE:</p> <p>11 Q. Okay.</p> <p>12 A. That doesn't mean it's the first drug that</p> <p>13 increases tear production. And it doesn't mean it's</p> <p>14 the first eye drop that, including nonprescription</p> <p>15 eye drops, that increase tear production.</p> <p>16 Q. Okay. But, again, my question was this:</p> <p>17 Restasis was the first drug that the FDA included a</p> <p>18 reference on the label as increasing</p> <p>19 tear production?</p> <p>20 A. Well, not to be argumentative, that was</p> <p>21 not your question; this is a new question phrased</p> <p>22 differently.</p> <p>23 And it was the first -- so what I'm</p> <p>24 alluding to is that there was at least one</p> <p>25 nonprescription drug that includes an ingredient</p> |
| <p style="text-align: right;">Page 47</p> <p>1 tear production?</p> <p>2 A. Well, with the caveats I've expressed. I</p> <p>3 mean, if I put every caveat in every sentence, the</p> <p>4 thing would be a hundred pages long.</p> <p>5 Q. Okay.</p> <p>6 A. But, yeah, I think we all understand these</p> <p>7 tests are imperfect, but they're common clinically</p> <p>8 performed tests that are reasonable proxies for</p> <p>9 these -- these entities -- these quantities.</p> <p>10 Q. And if we turn to paragraph 34 of your</p> <p>11 declaration, the last sentence is what I want to</p> <p>12 focus on here.</p> <p>13 A. I'm sorry. Which one?</p> <p>14 Q. The last one.</p> <p>15 A. Okay.</p> <p>16 Q. All right. And you say there that "The</p> <p>17 basal tear production as measured by the STT with</p> <p>18 anesthesia is highly relevant to patient symptoms"?</p> <p>19 A. Correct.</p> <p>20 Q. Okay. And then you continue on to say:</p> <p>21 "Total aqueous tear production capacity as measured</p> <p>22 by Schirmer tear without anesthesia also provides</p> <p>23 important information regarding the severity of the</p> <p>24 patient's dry eye condition," right?</p> <p>25 A. Correct.</p> | <p style="text-align: right;">Page 49</p> <p>1 that has been shown to increase tear production.</p> <p>2 But as far as prescription drugs that I'm aware that</p> <p>3 on the label it says "increases tear production,"</p> <p>4 I'm not aware of any other than Restasis.</p> <p>5 Q. Okay. Hand you, Dr. Calman, what's been</p> <p>6 previously marked as Exhibit 2008.</p> <p>7 Have you seen this before?</p> <p>8 A. Yes.</p> <p>9 Q. And what is your understanding of what</p> <p>10 this document is?</p> <p>11 A. This is at least a version of the FDA</p> <p>12 label for Restasis.</p> <p>13 Q. Okay. Do you know when Restasis was</p> <p>14 approved first by the FDA?</p> <p>15 A. Not exactly off the top of my head, but I</p> <p>16 think 2002.</p> <p>17 Q. Okay. And were you using Schirmer tear</p> <p>18 tests in your practice in 2002?</p> <p>19 A. Yes.</p> <p>20 Q. Okay. And were you using it to measure</p> <p>21 tear production in 2002?</p> <p>22 A. Tear production? Loosely speaking, yes.</p> <p>23 Q. All right. Hand you what's been marked as</p> <p>24 Exhibit 1007, Dr. Calman.</p> <p>25</p> |

| | |
|--|--|
| <p style="text-align: right;">Page 50</p> <p>1 Are you familiar with this document?</p> <p>2 A. Yes.</p> <p>3 Q. And do you understand this is the Sall</p> <p>4 paper that's been referred to in the proceedings?</p> <p>5 A. Yes.</p> <p>6 Q. And what do you understand this paper to</p> <p>7 be describing?</p> <p>8 A. This paper describes two Phase 3 pivotal</p> <p>9 trials of two different cyclosporin emulsions for</p> <p>10 treatment of moderate to severe KCS.</p> <p>11 Q. Okay. If we look at the second page,</p> <p>12 page 632, you see the section called "Materials and</p> <p>13 Methods"?</p> <p>14 A. Yes.</p> <p>15 Q. And there's a section in the middle of the</p> <p>16 right-hand column called "Study Medications"?</p> <p>17 A. Yes.</p> <p>18 Q. And you would agree that this paper</p> <p>19 describes that there was a 0.5 percent and a</p> <p>20 0.1 percent ophthalmic emulsion and vehicle that</p> <p>21 included cyclosporin A?</p> <p>22 MR. MILLS: Objection. Form.</p> <p>23 THE WITNESS: Well, the vehicle didn't</p> <p>24 include cyclosporin A. I would disagree with that</p> <p>25 part.</p> | <p style="text-align: right;">Page 52</p> <p>1 vehicle?</p> <p>2 A. Let me look a second.</p> <p>3 I don't see that explicitly stated.</p> <p>4 Q. In fact, it says that the castor oil in</p> <p>5 water emulsions were a proprietary formulation?</p> <p>6 MR. MILLS: Objection. Form.</p> <p>7 THE WITNESS: It says the precise</p> <p>8 formulation is proprietary.</p> <p>9 BY MR. KANE:</p> <p>10 Q. Okay. So there's nothing in Sall that</p> <p>11 tells you what the components in that proprietary</p> <p>12 formulation consist of?</p> <p>13 MR. MILLS: Objection. Form.</p> <p>14 THE WITNESS: Well, not explicitly in</p> <p>15 black and white words on paper, no.</p> <p>16 BY MR. KANE:</p> <p>17 Q. Okay.</p> <p>18 A. And, again, I think what we're talking</p> <p>19 about, if I'm assuming correctly when you say,</p> <p>20 "There's nothing that would tell you," I think you</p> <p>21 mean nothing to tell a person of ordinary skill in</p> <p>22 the art as of the priority date.</p> <p>23 Q. Yes. That's what --</p> <p>24 A. As of the priority date. I didn't hear</p> <p>25 what you said.</p> |
| <p style="text-align: right;">Page 51</p> <p>1 BY MR. KANE:</p> <p>2 Q. Okay. So there was a 0.5 percent CsA</p> <p>3 ophthalmic formulation?</p> <p>4 A. Yes.</p> <p>5 Q. And there was a 0.1 percent CsA ophthalmic</p> <p>6 emulsion formulation?</p> <p>7 A. Yes.</p> <p>8 Q. And then there was a vehicle?</p> <p>9 A. That's what's described.</p> <p>10 Q. Okay. And you'd agree that Sall does not</p> <p>11 describe what the vehicle used in the studies?</p> <p>12 A. Not --</p> <p>13 MR. MILLS: Objection. Form.</p> <p>14 THE WITNESS: Not explicitly.</p> <p>15 BY MR. KANE:</p> <p>16 Q. Okay. It doesn't -- it doesn't tell you</p> <p>17 how much castor oil is used in the vehicle?</p> <p>18 A. Not explicitly.</p> <p>19 Q. Does it tell how much surfactant is used</p> <p>20 in the vehicle?</p> <p>21 A. Not explicitly.</p> <p>22 Q. Does it describe the number of surfactants</p> <p>23 used in the vehicle?</p> <p>24 A. The what?</p> <p>25 Q. The number of surfactants used in the</p> | <p style="text-align: right;">Page 53</p> <p>1 Q. I was going to say, and so you've answered</p> <p>2 the questions with that understanding of my</p> <p>3 question?</p> <p>4 A. Well, the questions that you've asked me</p> <p>5 about Sall, yes.</p> <p>6 Q. Okay. So let's look at Figure 1 of Sall</p> <p>7 which is on page 635.</p> <p>8 A. Yes.</p> <p>9 Q. And this shows the results of the study</p> <p>10 formulations with respect to corneal staining.</p> <p>11 Do you see that?</p> <p>12 A. Yes.</p> <p>13 Q. And what does corneal staining indicate to</p> <p>14 a physician?</p> <p>15 A. Well, typically with corneal staining,</p> <p>16 most of the time you're using fluorescein,</p> <p>17 F-L-U-O-R-E-S-C-E-I-N. And basically you're</p> <p>18 instilling a fluorescein solution or using a</p> <p>19 fluorescein impregnated test strip to instill a</p> <p>20 small amount of dye in the eye. This dye has</p> <p>21 different colors depending on its concentration and</p> <p>22 depending on the underlying tissue, but typically</p> <p>23 it's orange.</p> <p>24 But if it adheres to devitalized spots or</p> <p>25 spots that are what we call epithelial defects on</p> |

| | |
|--|--|
| <p style="text-align: right;">Page 54</p> <p>1 the cornea, you will see a green glow or a green 2 spot when you illuminate it with cobalt blue light. 3 So it's a way of staining or identifying devitalized 4 or denuded, D-E-N-U-D-E-D, areas of the cornea. 5 Q. What is the clinical significance of 6 identifying those areas? 7 A. It's a proxy for basically an unhealthy 8 corneal or stressed epithelium, which is the outer 9 layer of the cornea, which is seen in various dry 10 eye conditions and other types of -- many other 11 types of eye conditions. 12 Q. Okay. But it provide a measure -- 13 A. I'm sorry. I'm just looking at the 14 transcript here. 15 It's a proxy for basically an unhealthy 16 corneal epithelium, E-P-I-T-H-E-L-I-U-M. 17 A proxy for -- maybe I shouldn't look at 18 this. 19 Q. Does it provide a measure of 20 tear production in the patient? 21 A. Not directly. 22 Q. Okay. And at six months, the 0.5 23 formulation was found to have been statistically 24 significantly better than vehicle? 25 A. I think you meant to say .05. And at six</p> | <p style="text-align: right;">Page 56</p> <p>1 than 0.5. -- .05 -- excuse me. 2 A. That is factually correct. I think the 3 way that most clinicians would interpret that and 4 that scientists would interpret that is that if you 5 set the level of significance at P equals .05, which 6 is a fairly standard level, with caveats that we 7 could perhaps discuss later, then this achieved 8 statistical significance for the .05 approached but 9 did not quite reach statistical significance for the 10 .1. 11 Q. Okay. 12 A. And if you look at the bar graph, that's 13 illustrated graphically. 14 And, you know, if you -- if you look at 15 the Month 4, you see a numerically better result 16 with the .1, although the difference between the 17 groups was not significant. And -- the difference 18 between significant -- between the .05 and the .1 19 was not reported as being significant at any time 20 point. 21 Q. But it's -- and at six months, the 22 0.05 percent was numerically superior to either -- 23 to both the 0.1 percent and the vehicle? 24 MR. MILLS: Objection. Form. 25 THE WITNESS: Numerically superior, yes.</p> |
| <p style="text-align: right;">Page 55</p> <p>1 months, both the .05 and -- well, first of all, to 2 state the data more completely for that time point, 3 all of the solutions, including vehicle, showed a 4 statistically significant improvement from baseline 5 at all follow-up visits including Month 6. 6 And the -- I believe that's correct. Let 7 me just double-check that. 8 Yes. "The improvement" -- and I'm reading 9 from the text here. "The improvement in corneal 10 staining was significantly greater in both CsA 11 groups than the vehicle group (P less than 0.044) at 12 Month 4, and in the CsA 0.05 percent group at 13 Month 6 (P equals 0.008)." 14 And then it also says -- let's see. 15 "There was also a trend (P equals 0.062) toward a 16 significantly greater improvement in the CsA 17 0.1 percent group than the vehicle group at Month 6 18 (Figure 1)." 19 That's a quotation from Sall, page 635. 20 And just to put this in context -- well, 21 I'll just stop there. 22 Q. Okay. And so what Sall, the portion you 23 just read, states is that the P value at Month 6 for 24 the 0.05 percent was less than .05, whereas the 25 P value for the 0.1 percent formulation was greater</p> | <p style="text-align: right;">Page 57</p> <p>1 Just as at Month 1, the .1 was numerically superior 2 to the other two. 3 BY MR. KANE: 4 Q. Okay. 5 A. And I'm not asserting that there's a 6 statistically significant difference between the .1 7 and .05 at Month 4, just that there is none at any 8 of the other time points, including Month 6. 9 Q. Okay. And then if we look at Sall 10 Figure 2, at three months the 0.05 percent 11 formulation has a P value of less than 0.5 compared 12 to vehicle, correct? 13 MR. MILLS: Objection. Form. 14 THE WITNESS: Well, I think you meant to 15 say .05. And to put that in context, this is 16 categorized Schirmer values with pitfalls that I 17 discussed at length, as did Dr. Bloch, in our 18 declarations, measured with anesthesia at the -- at 19 a time point that -- and which was measured only at 20 two time points in contrast to most of the other 21 measures. 22 And at the time point that was not the key 23 time point of six months as identified by Allergan, 24 none of these emulsions achieve any significant 25 change or seen -- none of these emulsions achieve a</p> |

| | |
|--|---|
| <p style="text-align: right;">Page 58</p> <p>1 significant change compared to baseline at Month 3.</p> <p>2 But there was a statistically significant</p> <p>3 difference between the .05 and vehicle but not</p> <p>4 between .05 and .1.</p> <p>5 So I think it's -- it's a big issue and</p> <p>6 can't be capsulized in one sentence.</p> <p>7 BY MR. KANE:</p> <p>8 Q. And, in fact, at Month 3, as reported in</p> <p>9 Sall, there was a significant worsening in patients</p> <p>10 treated with vehicle, correct?</p> <p>11 MR. MILLS: Objection. Form.</p> <p>12 THE WITNESS: Well, again, I think you're</p> <p>13 taking that out of context because if you look -- it</p> <p>14 was a result that's very odd. Because if you look</p> <p>15 at the Schirmer's without, which measures both basal</p> <p>16 and reflex to a first approximation, all of the</p> <p>17 groups, including the vehicle group, showed a</p> <p>18 statistically significant improvement at all time</p> <p>19 points. And they measured four time points: 1, 3,</p> <p>20 4, and 6.</p> <p>21 So how do you explain that the Schirmer's</p> <p>22 without anesthesia was statistically significantly</p> <p>23 increased at the same time point as the Schirmer's</p> <p>24 with anesthesia categorized would significantly</p> <p>25 decrease.</p> | <p style="text-align: right;">Page 60</p> <p>1 A. Yes. So, as I said, I can read -- of</p> <p>2 course, I can read that text there. And as a person</p> <p>3 of ordinary skill accustomed to reading scientific</p> <p>4 papers, I'm very troubled by this use of categorized</p> <p>5 Schirmer value, especially with these very broad</p> <p>6 categories and especially when changes -- small</p> <p>7 clinically insignificant changes up or down from</p> <p>8 baseline may have unpredictable effects on the</p> <p>9 score.</p> <p>10 For example, if you had a Schirmer of 3</p> <p>11 and you're in that Category 2, if you have a</p> <p>12 .1 millimeter decrease in Schirmer, that's going to</p> <p>13 show up as one unit decrease. If you have a 2.9 or</p> <p>14 even a 3-millimeter increase, it's not going to show</p> <p>15 up as a change at all.</p> <p>16 So it's a very strange way to obscure --</p> <p>17 well, to put an additional layer from the original</p> <p>18 data to what's being reported graphically here, that</p> <p>19 I don't understand why they did it. At least I</p> <p>20 don't agree with why they did it. And I think</p> <p>21 creates data points that just don't make sense in</p> <p>22 the overall context, particularly the Schirmer's</p> <p>23 without anesthesia, which showed an increase at all</p> <p>24 time points, four different time points with the</p> <p>25 vehicle.</p> |
| <p style="text-align: right;">Page 59</p> <p>1 So as a person of ordinary skill, when I</p> <p>2 look at that, I'm thinking this is very strange.</p> <p>3 And I would like to see the underlying raw Schirmer</p> <p>4 data, which we asked for which the patent owner did</p> <p>5 not want to disclose. But I would be surprised if</p> <p>6 the -- if the raw data would bear this out, and I</p> <p>7 would be surprised if Allergan had bothered to test</p> <p>8 this at other time points whether this decrease</p> <p>9 would -- would bear out.</p> <p>10 So I see that time point, that particular</p> <p>11 one data point out of this entire study where they</p> <p>12 studied 15 or 20 different efficacy variables, as an</p> <p>13 outlier. And -- and that is difficult to</p> <p>14 understand.</p> <p>15 BY MR. KANE:</p> <p>16 Q. Okay. But you agree that Schirmer states</p> <p>17 at Month 3 -- excuse me -- Sall states: "At</p> <p>18 Month 3, there was a significant worsening with the</p> <p>19 vehicle group (P equals 0.014) and a significant</p> <p>20 difference among the treatment groups?"</p> <p>21 A. I'm looking for that in the text. Can you</p> <p>22 point me to where that is?</p> <p>23 Q. Yes. It's above Sall Figure 2 there,</p> <p>24 middle of the first paragraph. Starts off "At</p> <p>25 Month 3."</p> | <p style="text-align: right;">Page 61</p> <p>1 So how do you explain that? And the</p> <p>2 authors couldn't and didn't. They didn't make any</p> <p>3 attempt to explain that.</p> <p>4 Q. Okay. But, again, my question is: Sall</p> <p>5 reports what it -- that there was a -- let me just</p> <p>6 read it.</p> <p>7 "At Month 3, there was a significant</p> <p>8 worsening with the vehicle group (P equals 0.014)</p> <p>9 and a significant difference among the treatment</p> <p>10 groups, with CsA 0.05 percent group significantly</p> <p>11 greater than the vehicle group (P equals 0.009)."</p> <p>12 Do you see that?</p> <p>13 A. I do see that, and I think I agree that I</p> <p>14 read that there. I just don't think that's the end</p> <p>15 of the analysis as a person of ordinary skill.</p> <p>16 Q. Okay.</p> <p>17 A. I agree that that sentence appears in the</p> <p>18 text there.</p> <p>19 Q. Okay. But you are choosing to reject that</p> <p>20 sentence?</p> <p>21 A. Well, it's not a matter of the choosing.</p> <p>22 It's a matter of applying the -- you know, applying</p> <p>23 the rest of the data set and other relevant data</p> <p>24 sets and my knowledge in reading and understanding</p> <p>25 clinical and scientific trials. I think it's an</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 62</p> <p>1 outlier.</p> <p>2 You know, I -- we -- we do use .05 P</p> <p>3 value. We use it a lot. It's a convenient P value.</p> <p>4 It's appropriate for a wide variety of tests, but</p> <p>5 it's not perfect.</p> <p>6 And, you know, there is a concept --</p> <p>7 there's a -- there's a concept called the Bonferroni</p> <p>8 correction, B-O-N-F-E-R-R-O-N-I, and other similar</p> <p>9 corrections which basically say when you're looking</p> <p>10 at 50 or 100 or 200 data points, some of them are</p> <p>11 going to come up as apparently statistically</p> <p>12 significant changes just by random chance.</p> <p>13 And, you know, if I have 20 types of jelly</p> <p>14 beans -- 20 different colors of jelly beans, and I</p> <p>15 distribute them to people with cancer, one of those</p> <p>16 20 is probably going to show statistically</p> <p>17 significant effect in curing cancer. Does that mean</p> <p>18 that grape jelly beans cure cancer? Probably not.</p> <p>19 If you repeated the test, you would probably not get</p> <p>20 that result.</p> <p>21 So, as scientists, we see this come up all</p> <p>22 the time. And so you look at and say that doesn't</p> <p>23 make sense physiologically, it doesn't make sense in</p> <p>24 the context of the rest of the data set, doesn't</p> <p>25 make sense in the context of other studies, and it</p> | <p style="text-align: right;">Page 64</p> <p>1 Q. At six months, the vehicle results shown</p> <p>2 in Schirmer tear -- excuse me -- in Figure 2 also</p> <p>3 show that the vehicle group was below baseline?</p> <p>4 A. Not to a statistically significant value.</p> <p>5 And, again, at the six-month time point as</p> <p>6 well as, just as at the one-, three-, and four-month</p> <p>7 time points, vehicle showed a statistically</p> <p>8 significant increase in baseline on Schirmer's</p> <p>9 without anesthesia, which measures total tear</p> <p>10 secretion ability. And not only that, there were no</p> <p>11 differences, no statistically significant</p> <p>12 differences between any of the formulations at any</p> <p>13 time point for Schirmer's without anesthesia.</p> <p>14 So, number one, I'd like to see the raw</p> <p>15 Schirmer data with anesthesia, both with and</p> <p>16 without, but especially with.</p> <p>17 And, number two, nobody has explained to</p> <p>18 me, either Sall and their co-authors, nor any of</p> <p>19 Allergan's experts, exactly how it is</p> <p>20 physiologically that supposedly this vehicle</p> <p>21 increases total tear production at the same time as</p> <p>22 it decreases basal tear production. That makes no</p> <p>23 sense. You know, it just doesn't make any sense</p> <p>24 based on anything that we have that we know.</p> <p>25 Q. Okay. But you agree with what's reported</p> |
| <p style="text-align: right;">Page 63</p> <p>1 can be explained as the fact that you're measuring a</p> <p>2 bunch of variables.</p> <p>3 It's as if your doctor ordered a panel of</p> <p>4 100 blood tests. Probably five of them are going to</p> <p>5 come back abnormal. If you retest them, they may</p> <p>6 not be abnormal but just on the basis of random</p> <p>7 chance.</p> <p>8 Q. Okay. You would agree -- and in this</p> <p>9 case, the P value compared between the 0.05 group</p> <p>10 and the vehicle at three months is .009.</p> <p>11 Do you see that?</p> <p>12 A. I see that. I'm not -- I'm not -- I</p> <p>13 haven't done my own calculation, but I'm not</p> <p>14 questioning their calculation.</p> <p>15 Q. Right.</p> <p>16 A. I'm just applying -- I'm putting it in</p> <p>17 context, and I won't repeat that whole last</p> <p>18 paragraph that I said.</p> <p>19 Q. Okay. So that's far below the P value of</p> <p>20 .05, true?</p> <p>21 A. Well, it's -- yeah, it's .014, which is</p> <p>22 less than .05.</p> <p>23 Q. I was actually pointing to the second P</p> <p>24 value, .009.</p> <p>25 A. .009 is also less than .05.</p> | <p style="text-align: right;">Page 65</p> <p>1 in Sall Figure 2?</p> <p>2 MR. MILLS: Objection.</p> <p>3 THE WITNESS: Well, I think I've answered</p> <p>4 that. I've tried to. I've explained that I can</p> <p>5 read the numbers on the page and I can put them in</p> <p>6 context, and that's what I've attempted to do.</p> <p>7 BY MR. KANE:</p> <p>8 Q. Okay.</p> <p>9 A. Well, you know, the other thing is --</p> <p>10 well, I'll just leave it at that.</p> <p>11 Q. And you agree that the data in Sall</p> <p>12 Figure 2 shows that the 0.5 is numerically superior</p> <p>13 to both the 0.1 percent formulation and the vehicle</p> <p>14 at six months?</p> <p>15 A. Well, I -- "numerically superior" is a</p> <p>16 little bit of a loaded term. It is not</p> <p>17 statistically significantly different.</p> <p>18 The number, the average number, the mean</p> <p>19 is higher. All of these are very small changes.</p> <p>20 But the number -- the change is slightly higher for</p> <p>21 the .05 on this particular time point.</p> <p>22 Q. You mentioned earlier that these are the</p> <p>23 categorized Schirmer scores, correct?</p> <p>24 A. Yes.</p> <p>25 Q. Do you know if the FDA relied upon</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 66</p> <p>1 categorized Schirmer scores in approving Restasis?</p> <p>2 A. So, again, using the available data for</p> <p>3 the IPR, I have not seen -- the only thing I have</p> <p>4 seen that is responsive to that question is --</p> <p>5 actually, let me just double-check one other thing</p> <p>6 here because I don't think there was a reference to</p> <p>7 the FDA in here.</p> <p>8 So I don't think there's anything in Sall</p> <p>9 that refers to the FDA.</p> <p>10 The label actually uses a different --</p> <p>11 different set of data or a different analysis of the</p> <p>12 data. It's not clear from, again, just using the</p> <p>13 documents available for the IPR.</p> <p>14 But what they are looking at -- let me</p> <p>15 find the correct part of this label -- is they're</p> <p>16 looking at a 10-millimeter increase in -- here it</p> <p>17 is. Page 5 of the FDA label.</p> <p>18 "Restasis demonstrated statistically</p> <p>19 significant increases in Schirmer wetting" --</p> <p>20 W-E-T-T-I-N-G -- "of 10 millimeters versus vehicle</p> <p>21 at six months in patients whose tear production was</p> <p>22 presumed to be suppressed due to ocular</p> <p>23 inflammation."</p> <p>24 Now, that's a little different from --</p> <p>25 that's a lot different, actually, from Sall because</p> | <p style="text-align: right;">Page 68</p> <p>1 that related to categorized Schirmer tests --</p> <p>2 categorized Schirmer values in approving Restasis?</p> <p>3 MR. MILLS: Objection. Form.</p> <p>4 THE WITNESS: I want to be careful here</p> <p>5 because I have been shown information in the</p> <p>6 district court case which is subject to protective</p> <p>7 order. And I've also seen some materials in the</p> <p>8 district -- some FDA documents in the district court</p> <p>9 case which may not be subjected -- subject to the</p> <p>10 protective order but which I have not considered for</p> <p>11 the IPR because I'm not sure that they were</p> <p>12 available to a POSA, P-O-S-A, as of the priority</p> <p>13 date. So I want to be careful in answering that</p> <p>14 question.</p> <p>15 Using the data set that -- that we've</p> <p>16 identified here -- and particularly the only FDA</p> <p>17 communication that I've identified is the FDA</p> <p>18 label -- there's nothing that suggests that they</p> <p>19 considered categorized Schirmer value.</p> <p>20 If you want me to go into information that</p> <p>21 I may be aware of from the district case, I would be</p> <p>22 very -- I think I would be very cautious about doing</p> <p>23 so.</p> <p>24 BY MR. KANE:</p> <p>25 Q. Okay.</p> |
| <p style="text-align: right;">Page 67</p> <p>1 it's not categorized, it's millimeters, which is how</p> <p>2 we as clinicians measure and interpret and read</p> <p>3 studies about Schirmer's. So it's not clear from...</p> <p>4 And then the vehicle -- sorry. "This</p> <p>5 effect was seen" -- I'm quoting: "This effect was</p> <p>6 seen in approximately 15 percent of Restasis</p> <p>7 ophthalmic emulsion-treated patients versus</p> <p>8 approximately 5 percent of the vehicle-treated</p> <p>9 patients. Increased tear production was not seen in</p> <p>10 patients currently taking topical anti-inflammatory</p> <p>11 drugs or using punctal" -- P-U-N-C-T-A-L -- "plugs."</p> <p>12 So it doesn't mention categorized, and it</p> <p>13 does mention Schirmer. And whether this patient</p> <p>14 population is the same as the patient population in</p> <p>15 Sall is not specified in the available documents.</p> <p>16 And I think that's the only reference to</p> <p>17 Schirmer, but let me just double-check that.</p> <p>18 So that is the only reference to Schirmer</p> <p>19 that I'm seeing just in rapidly skimming this FDA</p> <p>20 label.</p> <p>21 Q. Okay.</p> <p>22 A. If there are others, please point them</p> <p>23 out.</p> <p>24 Q. So, as you sit here today, you don't know</p> <p>25 whether the FDA relied on any of the Phase 3 data</p> | <p style="text-align: right;">Page 69</p> <p>1 A. I'm looking at the transcript. It says</p> <p>2 "to oppose a POSA." It supposed to say "to a POSA,"</p> <p>3 P-O-S-A.</p> <p>4 Q. Is it your understanding that unexpected</p> <p>5 results can only be shown by data that was available</p> <p>6 to a POSA as of the priority date?</p> <p>7 MR. MILLS: Objection. Form. Foundation.</p> <p>8 THE WITNESS: I think that's a legal</p> <p>9 question, not a -- not a medical or scientific</p> <p>10 question. And so I'm reluctant to give a definitive</p> <p>11 answer other than to say that what I have considered</p> <p>12 in my declaration is the information that has either</p> <p>13 been -- that was either clearly available to a POSA</p> <p>14 at the time of the priority date or that has been</p> <p>15 introduced and permitted by the PTAB.</p> <p>16 BY MR. KANE:</p> <p>17 Q. You don't have an opinion as to what</p> <p>18 information can be used from a legal perspective to</p> <p>19 show unexpected results?</p> <p>20 A. I don't have a definite enough</p> <p>21 understanding of that topic to express an opinion</p> <p>22 other than what may be in my -- let me just look at</p> <p>23 my...</p> <p>24 You know, Dr. Amiji may have addressed</p> <p>25 that as well because he had some information about</p> |

| | |
|--|---|
| <p style="text-align: right;">Page 70</p> <p>1 the legal framework in his -- let me look at mine 2 first. 3 I see in Dr. Amiji's declaration, 4 paragraph 29, it says: "The conclusion of 5 obviousness must be firmly based on the knowledge 6 and skill of a person of ordinary skill in the art 7 at the time the invention was made." 8 And there's a discussion of secondary 9 considerations in paragraphs 32 and 33 which do not 10 specifically address or answer that -- your 11 question. 12 The paragraph 34 also addresses the time 13 frame. 14 And let's see. One more place. 15 I need a minute to think. 16 I -- I'm thinking that in reading the 17 Schiffman and Attar declarations -- and, again, 18 although I'm somewhat reluctant to offer an opinion 19 that might verge on being a legal opinion -- my 20 understanding is that they offered their 21 declarations, which I do not have in front of me, 22 stating that there was new data to indicate that 23 the -- the claim formulation exhibited unexpected 24 results. 25 Now, as it happened, the new information</p> | <p style="text-align: right;">Page 72</p> <p>1 A. That is Exhibit 1040. 2 Q. If you'd turn to paragraph 77 of 3 Dr. Amiji's declaration for me. 4 A. Yes. 5 Q. And you see there's -- the second sentence 6 of that paragraph says: "At six months of 7 treatment, Figure 2 in Sall depicts a negative 8 change in Schirmer value (indicating worse dry eye 9 disease/KCS) and positive changes (indicating 10 improvement) for both CsA treatments, with the CsA 11 0.05 percent treatment having an average change in 12 Schirmer score more than one standard deviation 13 higher (better) than the CsA 0.1 percent treatment." 14 Do you see that? 15 A. I do see that. 16 Q. And do you agree with Dr. Amiji's 17 interpretation of Sall Figure 2? 18 A. Well, it's a literal -- it's a literal 19 statement that is not factually wrong. 20 The context that I would add in addition 21 to what I stated a few minutes ago is that -- 22 because, you know, there is no statistically 23 significant difference between the .01 -- the .1 and 24 the .05, and that the actual changes in Schirmer 25 score, which is about .3 to .4 units, those are very</p> |
| <p style="text-align: right;">Page 71</p> <p>1 that they offered was actually old information from 2 before the priority date. But the fact that they 3 offered supposedly new information would suggest to 4 me that at least Allergan's counsel was of the 5 opinion that information after the priority date 6 could be admissible for the purpose of unexpected 7 results. 8 But I say that just as a piece -- as a 9 data point, not that I'm expressing a conclusive 10 legal opinion on that because I'm not. 11 Q. Okay. So the record's clear, you've been 12 looking at the declaration of Dr. Amiji? 13 A. Yes, Amiji. 14 Q. Is that marked as Exhibit 1002? 15 A. It is, yes. This is actually -- yes, it 16 is. 17 Q. I see you've brought some other documents. 18 What other documents do you have with you? 19 A. I also have my declaration and Dr. Bloch's 20 declaration. And then you handed me my CV, the FDA 21 label, and Sall. 22 Q. Okay. What's -- 23 A. And another copy of my declaration. 24 Q. What's the exhibit number of Dr. Bloch's 25 declaration?</p> | <p style="text-align: right;">Page 73</p> <p>1 small and potentially, you know, either very mildly 2 clinically meaningful or not clinically meaningful. 3 So literally speaking, I agree with his 4 statement. 5 Q. Okay. 6 A. You know, I think, looking at it -- I'm 7 sorry. Looking at it more closely, I'm not sure 8 that he's demonstrated that it's more than one 9 standard deviation higher. I don't know that you 10 can do that just by looking at the graph. 11 Q. So you disagree with Dr. Amiji's 12 statement? 13 A. Well, I don't -- I don't -- I haven't done 14 a statistical analysis, and I don't know where he 15 got that conclusion. So I'm not agreeing or 16 disagreeing; I'm just saying I don't know for sure 17 if that is correct. 18 Q. Okay. If we look at Sall on page 637, 19 please. 20 And there's a paragraph in the middle of 21 the page. It begins "This study." 22 A. Uh-huh. 23 Q. Do you see that? 24 This paragraph is talking about 25 improvements in categorized Schirmer value obtained</p> |

| | |
|--|---|
| <p style="text-align: right;">Page 74</p> <p>1 with anesthesia?</p> <p>2 A. Yes.</p> <p>3 Q. And it says -- the concluding sentence</p> <p>4 says: "Consequently, the results presented here</p> <p>5 suggests that the CsA treatment is affecting</p> <p>6 baseline tearing, not reflexive tearing."</p> <p>7 Do you see that?</p> <p>8 A. I see that.</p> <p>9 Q. Okay. And do you agree with that</p> <p>10 interpretation of Sall?</p> <p>11 A. It's -- it doesn't explain all of the</p> <p>12 data. I -- I don't understand how, for example,</p> <p>13 if -- you know, again, I think there's some --</p> <p>14 there's some issues with the data set, particularly</p> <p>15 the three-month figures for the .1 percent. Why</p> <p>16 would it go down at three months and go up -- why</p> <p>17 would the, quote/unquote, basal the category</p> <p>18 Schirmer with anesthesia go down at three months</p> <p>19 when the categorized Schirmer without anesthesia</p> <p>20 goes up at the same time point? That would suggest</p> <p>21 basal tearing went down and reflex tearing went up.</p> <p>22 And how do you explain that?</p> <p>23 And similarly -- and then how do you</p> <p>24 explain that that's not -- you know, that that's</p> <p>25 also the effect with the castor oil at three months?</p> | <p style="text-align: right;">Page 76</p> <p>1 BY MR. KANE:</p> <p>2 Q. Okay. All right. Let's look at Figure 3.</p> <p>3 And this is measuring change from baseline in</p> <p>4 blurred vision.</p> <p>5 Do you see that?</p> <p>6 A. Yes.</p> <p>7 Q. And how do you measure blurred vision in</p> <p>8 patients with dry eye disease?</p> <p>9 A. So -- well, how do I measure it or how did</p> <p>10 they measure it?</p> <p>11 Q. How did they measure it?</p> <p>12 A. Well, they measured it, at least on this</p> <p>13 particular one that they're reporting, it appears to</p> <p>14 be a subjective patient-reported zero to 4 scale.</p> <p>15 It was one of many, many subjective symptoms that</p> <p>16 they measured, including -- and I reviewed them at</p> <p>17 length in my declaration.</p> <p>18 So this is only one of a lot, including</p> <p>19 OSDI, subjective facial expression rating scale,</p> <p>20 stinging and burning, itching, sandiness and</p> <p>21 grittiness, blurred vision, dryness, light</p> <p>22 sensitivity, pain, soreness, investigator's global</p> <p>23 evaluation, patient use of artificial tears, number</p> <p>24 of artificial tears per day. Number of days per</p> <p>25 week that they did not use the tears.</p> |
| <p style="text-align: right;">Page 75</p> <p>1 So, you know, I think they're making this</p> <p>2 conclusion, and they probably had some access to the</p> <p>3 raw Schirmer data which we do not have in this</p> <p>4 article. So I -- I think the data set raises some</p> <p>5 questions in addition to the sort of pat answer.</p> <p>6 And the other thing that I would say is</p> <p>7 that they have not given us any actual numbers for</p> <p>8 Schirmer's without anesthesia. So it may be that</p> <p>9 cyclosporin is affecting both baseline and reflexive</p> <p>10 tearing, but they have not shown their work so we</p> <p>11 don't know. We just have this sentence.</p> <p>12 And -- you know, again, I think if we</p> <p>13 could get our hands on the NDA actual data in</p> <p>14 millimeters, which is the way the data were</p> <p>15 collected and the way that the clinicians used the</p> <p>16 test, it might clarify some of these apparent</p> <p>17 disparities.</p> <p>18 Q. Okay. But you do agree that the authors</p> <p>19 of the paper reached the conclusion that the CsA</p> <p>20 treatment is affecting the baseline tearing and not</p> <p>21 reflexive tearing?</p> <p>22 MR. MILLS: Objection. Form.</p> <p>23 THE WITNESS: That's one of the things</p> <p>24 that they say. They say a lot of things. But that</p> <p>25 sentence does appear in there.</p> | <p style="text-align: right;">Page 77</p> <p>1 So there's a lot of these subjective</p> <p>2 measures. They chose to emphasize this one in the</p> <p>3 graph, but there were a whole bunch of them and...</p> <p>4 So that's, you know -- and as far as I can</p> <p>5 tell from what's provided in the "Materials and</p> <p>6 Methods" section, this was the patient self-reported</p> <p>7 zero to 4 for scale, "Doc, my eyes aren't blurry at</p> <p>8 all. Doc, my eyes are really blurry." That's a 4</p> <p>9 presumably.</p> <p>10 I mean, how do we measure it in the</p> <p>11 clinic? We determine a best corrected visual</p> <p>12 acuity.</p> <p>13 Q. Have you ever been involved in the design</p> <p>14 of a Phase 3 study?</p> <p>15 A. You know, I was certainly involved in</p> <p>16 discussions with investigators who were doing</p> <p>17 Phase 3 studies, and I don't remember exactly at</p> <p>18 what stage.</p> <p>19 Q. Have you ever been involved in discussions</p> <p>20 with the FDA in design of a Phase 3 study?</p> <p>21 A. Directly with the FDA, no.</p> <p>22 Q. Okay. You would agree that, in Figure 3,</p> <p>23 the 0.05 percent formulation is numerically superior</p> <p>24 at all time frames?</p> <p>25 MR. MILLS: Objection. Form.</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 78</p> <p>1 THE WITNESS: Well, if you put it in</p> <p>2 context, this one of more than a dozen subjective</p> <p>3 measures shows numeric superiority showing small</p> <p>4 changes of .3 to .5 units on a zero to 4 scale at</p> <p>5 all time points.</p> <p>6 BY MR. KANE:</p> <p>7 Q. Okay. Is change baseline -- excuse me.</p> <p>8 Is change in blurred vision a measure of</p> <p>9 increased tear production?</p> <p>10 A. Well, you know, blurred vision can be</p> <p>11 caused by a lot of things. However, certainly one</p> <p>12 of many factors that can affect blurred vision is</p> <p>13 tear production. But it is, at best, an indirect</p> <p>14 measure.</p> <p>15 Q. Does it provide any sort of quantification</p> <p>16 of increased tear production?</p> <p>17 A. I think that would be a stretch.</p> <p>18 Q. Does that mean no?</p> <p>19 A. I think that would be a stretch.</p> <p>20 Q. What do you mean when you say it would be</p> <p>21 a stretch?</p> <p>22 A. Well, I think that it would be a stretch</p> <p>23 to say decreased blurred vision implies increased</p> <p>24 tear production, although in many cases, many</p> <p>25 patients -- increased tear production across -- as a</p> | <p style="text-align: right;">Page 80</p> <p>1 typically use their artificial tears more</p> <p>2 frequently.</p> <p>3 Now, that said, this graph, I believe, was</p> <p>4 disavowed because it appears to be a copy of</p> <p>5 Figure 3, which was probably just a -- an error in</p> <p>6 production of this paper.</p> <p>7 Q. Yeah. Okay. But --</p> <p>8 A. But I think I've answered your question</p> <p>9 too.</p> <p>10 Q. Yes. Exactly.</p> <p>11 I think in paragraph 58 of your</p> <p>12 declaration, Dr. Calman --</p> <p>13 A. I'm going to ask that we take a break very</p> <p>14 soon.</p> <p>15 Q. Why don't we just take it right now.</p> <p>16 (Off the record at 11:07 a.m. and back</p> <p>17 on the record at 11:21 a.m.)</p> <p>18 BY MR. KANE:</p> <p>19 Q. All right. I think we were going to</p> <p>20 paragraph 58 of your declaration, Exhibit 1039.</p> <p>21 A. Yes.</p> <p>22 Q. Okay. And we -- you go through a list of</p> <p>23 the parameters that were considered in the Allergan</p> <p>24 Phase 3 study disclosed in Sall.</p> <p>25 Do you see that?</p> |
| <p style="text-align: right;">Page 79</p> <p>1 blanket statement, although that may be true for</p> <p>2 some of these patients.</p> <p>3 Q. And let's look at Figure 4 in Sall.</p> <p>4 A. Yes.</p> <p>5 Q. This is change in baseline in average</p> <p>6 daily use of artificial tears.</p> <p>7 Do you see that?</p> <p>8 MR. MILLS: Objection. Form.</p> <p>9 THE WITNESS: Well, there are some issues</p> <p>10 with this graph that maybe we can talk about. It</p> <p>11 does say that, yes.</p> <p>12 BY MR. KANE:</p> <p>13 Q. Okay. And is a change in baseline in</p> <p>14 average daily use of artificial tears a direct</p> <p>15 measure of increased tear production?</p> <p>16 A. Not a direct measure, no.</p> <p>17 Q. Okay. Okay. Is it a -- well, is it a</p> <p>18 stretch again?</p> <p>19 A. Well, it's a less of a stretch because</p> <p>20 there are a lot more things that cause blurred</p> <p>21 vision than there are that cause people to use their</p> <p>22 tears more often.</p> <p>23 Again, it's not a direct measure but,</p> <p>24 generally speaking, if -- if you have a group of</p> <p>25 people who have lower tear production, they will</p> | <p style="text-align: right;">Page 81</p> <p>1 A. I go through a variety of the efficacy</p> <p>2 outcome measures, yes.</p> <p>3 Q. I think we've already talked about the</p> <p>4 corneal staining in connection with the Figure 1, so</p> <p>5 I'll move past that.</p> <p>6 The next one is conjunctival staining.</p> <p>7 Would you agree that that does not directly measure</p> <p>8 increased basal tear production?</p> <p>9 A. Well, it's a very important outcome for</p> <p>10 dry eyes because it's a measure of devitalized</p> <p>11 conjunctiva at the ocular surface.</p> <p>12 And so, although there may be a</p> <p>13 correlation with basal tear production, it is not</p> <p>14 a -- it is not a direct measure of basal</p> <p>15 tear production.</p> <p>16 Q. Okay. And then we've already talked at</p> <p>17 length about Schirmer tear with anesthesia and</p> <p>18 Schirmer tear without anesthesia. So we can move</p> <p>19 past that.</p> <p>20 Blurred vision, we've talked about.</p> <p>21 Dryness. Would you agree dryness is not</p> <p>22 a measure of increased basal tear production?</p> <p>23 A. Well, first of all, dryness here, as I</p> <p>24 understand it reading "Materials and Methods"</p> <p>25 section is a patient's subjective self-assessment of</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 82</p> <p>1 how dry their eyes feel. And, again, I think there</p> <p>2 is a correlation between that and basal</p> <p>3 tear production in this type of patient, but it is</p> <p>4 not a direct measure of basal tear production.</p> <p>5 Q. Next listed here is a sandy, gritty</p> <p>6 feeling.</p> <p>7 Do you see that?</p> <p>8 A. Yes.</p> <p>9 Q. And would you agree that a sandy, gritty</p> <p>10 feeling is not a direct measure of increased basal</p> <p>11 tear production?</p> <p>12 A. It would be my same answer. This is,</p> <p>13 again, a subjective self-assessment of sandy and</p> <p>14 gritty feeling in the patient's eye. And although</p> <p>15 it's an important symptom and it tends to correlate</p> <p>16 with basal tear secretion in this type of patient,</p> <p>17 it is not a direct measurement of basal tear</p> <p>18 secretion.</p> <p>19 Q. Next is itching.</p> <p>20 Do you see that?</p> <p>21 A. I do.</p> <p>22 Q. And would you agree that itching is not a</p> <p>23 direct measurement of increased basal tear</p> <p>24 secretion?</p> <p>25 A. So similar answer. I think this is a</p> | <p style="text-align: right;">Page 84</p> <p>1 common symptoms in patients with various dry eye</p> <p>2 conditions as well as some other ocular conditions.</p> <p>3 And that although they do tend to correlate with</p> <p>4 basal tear secretion in this type of patient, they</p> <p>5 are not a direct measurement of basal tear</p> <p>6 secretion.</p> <p>7 Q. Next is pain.</p> <p>8 Do you see that?</p> <p>9 A. I do.</p> <p>10 Q. And do you agree that pain is not a direct</p> <p>11 measurement of increased basal tear secretion?</p> <p>12 A. So pain, I would say, is also an important</p> <p>13 symptom in this type of patient, although it can be</p> <p>14 seen with many other types of ocular conditions. In</p> <p>15 my experience, this is -- this does correlation well</p> <p>16 with basal tear secretion but it is not a direct</p> <p>17 measurement.</p> <p>18 And this is one of the parameters where</p> <p>19 the .1 percent performed numerically better than the</p> <p>20 .05 percent.</p> <p>21 Q. Okay. Next is the physician's subjective</p> <p>22 assessment of global response to treatment.</p> <p>23 Do you see that?</p> <p>24 A. I do.</p> <p>25 Q. And would you agree that that measure is</p> |
| <p style="text-align: right;">Page 83</p> <p>1 common symptom in patients with dry eye and other</p> <p>2 ocular surface conditions, including blepharitis,</p> <p>3 B-L-E-P-H-A-R-I-T-I-S.</p> <p>4 And in this type of patient, it does tend</p> <p>5 to correlate with basal tear secretion, but it is</p> <p>6 not a direct measurement of basal tear secretion.</p> <p>7 Q. Next is photophobia.</p> <p>8 Do you see that?</p> <p>9 A. Yes.</p> <p>10 Q. And would you agree that photophobia is</p> <p>11 not a direct measurement of increased basal</p> <p>12 tear production?</p> <p>13 A. I would say that photophobia is a less</p> <p>14 common symptom seen in some dry eye patients and</p> <p>15 also seen in many, many other types of conditions.</p> <p>16 And that although this in type of patient there may</p> <p>17 be some correlation between photophobia and basal</p> <p>18 tear secretion, it is not a direct measurement of</p> <p>19 basal tear secretion.</p> <p>20 Q. Next is burning and stinging.</p> <p>21 Do you see that?</p> <p>22 A. I do.</p> <p>23 Q. Would you agree that burning and stinging</p> <p>24 is not a direct measurement of basal tear secretion?</p> <p>25 A. I would say that these are important and</p> | <p style="text-align: right;">Page 85</p> <p>1 not a direct measure of increased basal tear</p> <p>2 secretion?</p> <p>3 A. So this -- now we're shifting to the</p> <p>4 physician's assessment. And although it says</p> <p>5 "subjective," it is the physician's overall</p> <p>6 impression as defined in more detail in the</p> <p>7 "Materials and Methods" of the patient's response</p> <p>8 overall to treatment.</p> <p>9 And in my experience this would correlate</p> <p>10 fairly well with basal tear secretion in this</p> <p>11 patient population with this type of problem, but it</p> <p>12 is not a direct measurement of basal tear secretion.</p> <p>13 I would point out again this is another</p> <p>14 area of where the .1 percent had some numerical</p> <p>15 superiority.</p> <p>16 Q. And we've talked already about artificial</p> <p>17 tear use. We can skip that.</p> <p>18 The next then in the listing is Ocular</p> <p>19 Surface Disease Index.</p> <p>20 Do you see that?</p> <p>21 A. I do.</p> <p>22 Q. And would you agree that Ocular Surface</p> <p>23 Disease Index is not a direct measurement of basal</p> <p>24 tear secretion?</p> <p>25 A. The Ocular Surface Disease Index, as I</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 86</p> <p>1 understand it, is a patient questionnaire with a</p> <p>2 variety of questions relevant to patients with</p> <p>3 dry eye symptoms. And although in my experience it</p> <p>4 does correlate well with basal tear secretion in</p> <p>5 this patient population, it is not a direct</p> <p>6 measurement of -- of basal tear secretion.</p> <p>7 Q. And then finally, subjective facial</p> <p>8 expression rating scale.</p> <p>9 Do you see that?</p> <p>10 A. I do.</p> <p>11 Q. Do you agree that the subjective facial</p> <p>12 rating scale is not a direct measurement of</p> <p>13 increased basal tear secretion?</p> <p>14 A. So the subjective facial rating schedule</p> <p>15 is basically a patient self-rating of whether</p> <p>16 they're happy or sad according to their symptoms</p> <p>17 related to dry eye. And although there is some</p> <p>18 correlation, in my experience, between this type of</p> <p>19 self-evaluation and basal tear secretion, I would</p> <p>20 not say that it is a direct measurement of basal</p> <p>21 tear secretion.</p> <p>22 Q. If we look at -- take a quick look at</p> <p>23 Exhibit 2008.</p> <p>24 A. I'm not sure what that is.</p> <p>25 Q. It's the FDA label for Restasis.</p> | <p style="text-align: right;">Page 88</p> <p>1 even smaller minority of vehicle patients -- treated</p> <p>2 patients got it.</p> <p>3 But, you know, what I do know is that the</p> <p>4 FDA looks at a large body of information when they</p> <p>5 make a decision on approval, and it's generally not</p> <p>6 just one thing. They look at a variety of</p> <p>7 parameters to determine whether a drug is safe and</p> <p>8 effective.</p> <p>9 And although I cannot get inside of the</p> <p>10 mind of the FDA and I'm not relying on any materials</p> <p>11 that would not have been available through a POSA at</p> <p>12 that time, I would be surprised if that were the</p> <p>13 only piece of information that they considered.</p> <p>14 Although they cite it, so I presume it was a</p> <p>15 material aspect that they considered.</p> <p>16 BY MR. KANE:</p> <p>17 Q. Okay. We've just gone through this sort</p> <p>18 of laundry list in paragraph 58 of other efficacy</p> <p>19 measures.</p> <p>20 Does the FDA mention any of those efficacy</p> <p>21 measures on page 5 of 2008?</p> <p>22 MR. MILLS: Objection. Form.</p> <p>23 THE WITNESS: Well, you're asking me is it</p> <p>24 on the label, and this is a very brief document.</p> <p>25 So in this particular document -- I can</p> |
| <p style="text-align: right;">Page 87</p> <p>1 A. Okay.</p> <p>2 Q. If we look at what we had seen previously</p> <p>3 on page 5.</p> <p>4 Do you see that?</p> <p>5 A. Okay. I'm on page 5.</p> <p>6 Q. Okay. Isn't it true that the FDA relied</p> <p>7 only on the Schirmer wetting of greater than 10</p> <p>8 millimeters in describing the studies that they base</p> <p>9 their approval upon?</p> <p>10 MR. MILLS: Objection. Form.</p> <p>11 THE WITNESS: You're asking me to get</p> <p>12 inside the mind of the FDA which I can't -- cannot</p> <p>13 do with this one paragraph. This is a piece of</p> <p>14 information that they cite. And, again, I want to</p> <p>15 be careful not to get into information that is not</p> <p>16 within the scope of a POSA at the priority date.</p> <p>17 However, there are some exhibits, other</p> <p>18 exhibits in evidence, where they talked about the</p> <p>19 failure of Restasis to be approved in 1999 and the</p> <p>20 relative success of the vehicle. And, you know,</p> <p>21 ultimately they got approved in 2002, presumably --</p> <p>22 again, as a POSA in 2003 looking at this, I would</p> <p>23 say well presumably, the FDA was impressed by this</p> <p>24 10-millimeter increase even though only a small</p> <p>25 minority of Restasis-treated patients got it and an</p> | <p style="text-align: right;">Page 89</p> <p>1 read as well as you can -- it doesn't state anything</p> <p>2 about those, at least on this page 5. If you'd like</p> <p>3 me to go through the rest of it, I will.</p> <p>4 BY MR. KANE:</p> <p>5 Q. No, that's fine. Thank you.</p> <p>6 A. Again, I don't think that's the sum total</p> <p>7 of what the FDA reviewed.</p> <p>8 Q. If we go to paragraph 67 of your</p> <p>9 declaration, Dr. Calman.</p> <p>10 A. Uh-huh.</p> <p>11 Q. In this section sort of 67 through 71 --</p> <p>12 A. Yes.</p> <p>13 Q. -- you attempt to infer from values from</p> <p>14 Sall Figure 2.</p> <p>15 Do you see that?</p> <p>16 A. Well, that's not quite right.</p> <p>17 Q. Well, that -- for instance, paragraph 68,</p> <p>18 above the graph there, you say: "These putative</p> <p>19 conversions are meant to be used in inferring</p> <p>20 differences from baseline?"</p> <p>21 A. Rather than -- yes. "These putative</p> <p>22 conversions are meant to be used in inferring</p> <p>23 differences from baseline, rather than interpreted</p> <p>24 as literal conversions (which would ultimately</p> <p>25 require that Allergan provide the raw data)."</p> |

| | |
|---|---|
| <p style="text-align: right;">Page 90</p> <p>1 That's what it says.</p> <p>2 Q. Okay. And have you ever done this sort of</p> <p>3 inferring differences in analyzing scientific data</p> <p>4 before?</p> <p>5 A. Sure.</p> <p>6 Q. Have you published any papers where you've</p> <p>7 done such a thing?</p> <p>8 A. No, not that I can recall. I may have.</p> <p>9 Many of my papers were published many years ago.</p> <p>10 Scientists interpret data all the time.</p> <p>11 Q. I'm talking about specifically this sort</p> <p>12 of interpretation where you're taking a bar chart</p> <p>13 and concluding and changing it into these</p> <p>14 conversions to infer differences from baseline.</p> <p>15 A. Doctors and scientists convert things all</p> <p>16 the time, even as simple things as converting</p> <p>17 different units and different scales. You know, for</p> <p>18 example, the Stevenson paper used a zero to 3 scale</p> <p>19 for corneal staining, and the Sall paper used a zero</p> <p>20 to 5 scale.</p> <p>21 People are constantly coming up with new</p> <p>22 classification schemes and scales and gradings and</p> <p>23 cutoffs for all kinds of parameters throughout</p> <p>24 medicine and science. So this is a common issue</p> <p>25 that we run into.</p> | <p style="text-align: right;">Page 92</p> <p>1 Q. Can you identify any of those papers</p> <p>2 today?</p> <p>3 A. I haven't thought about it. I haven't</p> <p>4 been asked to opine on it. It's not something I've</p> <p>5 given any thought to. You know, there's so many --</p> <p>6 I'll probably think of 10 examples when I leave</p> <p>7 but...</p> <p>8 Q. If you look at -- if we go back to</p> <p>9 paragraph 67, please.</p> <p>10 A. Okay.</p> <p>11 Q. There's a description there. It says:</p> <p>12 "Sall Figure 2 demonstrates the average change in</p> <p>13 Schirmer score experienced at Month 3 was actually</p> <p>14 very small for both CsA groups with patients in the</p> <p>15 0.05 percent CsA group experiencing a plus 0.09</p> <p>16 change in Schirmer score" -- "categorized score" --</p> <p>17 excuse me -- "versus minus 0.10 for patients in the</p> <p>18 0.1 percent CsA group."</p> <p>19 Do you see that?</p> <p>20 A. I see where it says that.</p> <p>21 Q. Okay. And did you determine those</p> <p>22 numbers?</p> <p>23 A. Well, I cite to Bloch actually. I can</p> <p>24 eyeball it, but that's not a -- I wouldn't up come</p> <p>25 up with a precise number like that for my modeling.</p> |
| <p style="text-align: right;">Page 91</p> <p>1 And the attempt -- again, I wanted -- I</p> <p>2 qualified it in the text. I'm not saying this is a</p> <p>3 literal conversion. This is an attempt to</p> <p>4 understand what these arbitrary units mean,</p> <p>5 especially since it's sort of a strange way and</p> <p>6 uncommon way to, you know, to treat Schirmer data.</p> <p>7 So they're reporting certain changes.</p> <p>8 Their -- I think most of the reporting was done in</p> <p>9 the form of change analysis. I'm trying to</p> <p>10 understand what do these changes mean, how big are</p> <p>11 they, and are they clinically material.</p> <p>12 Of course, if I had the raw data which we</p> <p>13 asked for repeatedly, it would have been much easier</p> <p>14 to use the raw data but we couldn't get it.</p> <p>15 Q. Have you ever seen any papers where</p> <p>16 there's been a conversion -- putative conversion</p> <p>17 published like this?</p> <p>18 A. I'm sure I have. I can't give you chapter</p> <p>19 and verse. I haven't seen -- I haven't for</p> <p>20 Schirmer's because I don't believe -- I can't recall</p> <p>21 any papers that I've seen other than Sall and</p> <p>22 Stevenson where categorized Schirmer's were</p> <p>23 reported.</p> <p>24 Q. Okay.</p> <p>25 A. But in other areas of science, sure.</p> | <p style="text-align: right;">Page 93</p> <p>1 I was relying on Bloch, who has a methodology to</p> <p>2 determine that more precisely.</p> <p>3 Q. And what do you understand Dr. Bloch did</p> <p>4 to determine those numbers?</p> <p>5 A. I would be hesitant to put words in his</p> <p>6 mouth. But my understanding is it involved</p> <p>7 magnifying the graph and measuring the height of the</p> <p>8 bars and standard deviation or standard error bars.</p> <p>9 Q. And is that something that you have done</p> <p>10 in your analysis of peer-reviewed papers that you've</p> <p>11 reviewed previously?</p> <p>12 A. I don't know if I've actually magnified</p> <p>13 them. I probably have from time to time just</p> <p>14 informally for myself to get a better idea of the</p> <p>15 numeric data when the data were not directly cited.</p> <p>16 Q. Okay. And you think that you could</p> <p>17 measure to two decimal points using a magnifying</p> <p>18 glass and a ruler, I guess, of some type?</p> <p>19 A. Well, that's a very broad statement. I</p> <p>20 think that would depend on a lot of factors.</p> <p>21 Q. Okay. Well, let's look at Sall --</p> <p>22 A. Incomplete.</p> <p>23 Q. Can we look at Sall Figure 2?</p> <p>24 Do you think you could measure those</p> <p>25 values to two decimal points?</p> |

| | |
|--|--|
| <p style="text-align: right;">Page 94</p> <p>1 A. It's not a question I was asked to opine 2 on; it's a question I've thought about. And so the 3 best answer I can give you is maybe. If I were 4 really to analyze that, I would probably, you know, 5 need to do some additional research and -- you know, 6 so I can't give you an answer other than maybe. 7 Q. Okay. Do you know how accurate graphs in 8 the publications are? 9 A. Well, that's a very broad and very 10 nonspecific question, so I can't give you a specific 11 answer to such a vague question. 12 Q. Would you base a conclusion based strictly 13 on measuring a graph in a publication? 14 A. Again, it's a very vague and broad 15 question. It's an incomplete hypothetical. 16 And so in some situations, you might. Of 17 course, all of this could be avoided if Allergan 18 would produce the actual data. 19 Q. Okay. You relied on Dr. Bloch's 20 measurements in this case, correct? 21 A. For that particular thing, yes. 22 Q. Yeah. So -- and that underlies your 23 opinion, correct? 24 A. Well, to the extent that I relied on it in 25 that particular part of my -- my declaration, yes.</p> | <p style="text-align: right;">Page 96</p> <p>1 that -- that we're even talking about those 2 particular numbers in this particular part of my 3 declaration, and, you know, frankly, I don't know 4 why we're quibbling over this because even if there 5 were a small error because of either the journal 6 making an error or the -- or Dr. Bloch not being 7 able to estimate with a certain degree of precision, 8 my point in this is these differences are small. If 9 you told me he was off by 50 percent, it wouldn't 10 change my conclusion that these differences are 11 small. 12 I don't care if it's one, two, or three 13 significant digits. It wouldn't materially affect 14 my conclusions. 15 Q. Okay. 16 A. And what I can provide that Dr. Bloch 17 doesn't provide is the clinical context. And I can 18 say that a difference of 1 or 2 or even 3 19 millimeters is not a big difference in Schirmer 20 scores clinically. A difference of 10 is. 21 Q. Uh-huh. 22 A. And that's what I say in my declaration. 23 Q. Okay. And if we -- let's compare your 24 table on paragraph 68 to Sall Figure 2. 25 And we see in Sall Figure 2 there's going</p> |
| <p style="text-align: right;">Page 95</p> <p>1 Q. So, in this case, you believe that 2 Dr. Bloch's two decimal places is sufficiently 3 accurate that you can rely upon it? 4 A. Well, hang on. First of all, I'm not sure 5 where you're getting two significant digits, so I'm 6 not sure I can accept the premise of your question. 7 Q. Well -- 8 A. Which paragraph are we on? 9 Q. Paragraph 67. 10 A. So when you say -- okay. So the .09 has 11 only one significant digit. .10 has two significant 12 digits. 13 These are questions that I think you 14 should be asking Dr. Bloch. Dr. Bloch is one of the 15 most eminent biostatisticians in the world, is my 16 understanding. 17 And so you're asking me to question his 18 methodology. I think I'm the wrong person to ask 19 those questions. I rely on him because of his 20 expertise and stature, and if he says that he can 21 determine these to that degree of precision and 22 accuracy, I do not have reason to question him. 23 Q. And because of that, you felt comfortable 24 relying on that in your analysis? 25 A. You know, I'm not -- again, to the extent</p> | <p style="text-align: right;">Page 97</p> <p>1 to be a value of 3 assigned to all scores between 7 2 and 10 millimeters. 3 Do you see that? 4 A. I do. 5 Q. Okay. And then we compare your table. 6 You have a score of 3 assigned to 7. You have a 7 score of 3.25 assigned to 8. You have a score of 8 3.5 assigned to 9. And you have a score of 3.75 9 assigned to 10. 10 Do you see that? 11 A. Yeah. But the context, again -- I have to 12 remind you -- is what I said at the outset of this 13 analysis, is it's -- we read it into the record 14 already -- that these putative conversions -- "These 15 putative conversions are meant to be used in 16 inferring differences" -- underlined "differences," 17 I'm underlining it in my -- what I'm saying now -- 18 "from baseline, rather that are interpreted as 19 literal conversions (which would ultimately require 20 that Allergan provide the raw data)." 21 Q. Uh-huh. 22 A. And Figure 2 is a different plot. I'm not 23 saying that a Schirmer score of 2 is literally 24 3 millimeters. 25 I'm saying that if you're in that range of</p> |

| | |
|--|--|
| <p style="text-align: right;">Page 98</p> <p>1 around 2 and you have a plus .1 putative difference, 2 what does that equate to in terms of millimeters of 3 change from baseline? And that's what I'm focused 4 on. 5 And so I don't care if you arbitrarily 6 adjust these and quibble a little bit over whether 7 it's -- whether a score of 2 is 3 millimeters or 4 8 millimeters or 5 millimeters. It doesn't really 9 materially affect my analysis because what I'm 10 looking for is the difference between the baseline 11 and post-treatment. 12 Q. But you agree that the values you've 13 assigned are different than the values in Sall 14 Figure 2? 15 MR. MILLS: Objection. Foundation. 16 Mischaracterization. 17 THE WITNESS: Totally mischaracterizes 18 what I said. I'm just going to defer to my previous 19 answer. 20 These are -- the ranges were set up by 21 this group of doctors, this group of investigators. 22 What I'm trying to do is say how do these 23 differences in arbitrary categorized units as a mean 24 of a population translate to changes in actual 25 Schirmer data in millimeters, which is how we do the</p> | <p style="text-align: right;">Page 100</p> <p>1 Q. Okay. And I'll just tell you that the 2 PTAB denied Mylan's request for the data. They 3 didn't feel that you needed it. 4 MR. MILLS: Objection. Foundation. 5 Mischaracterization. 6 THE WITNESS: Well, I'm not going to 7 respond to that. It wasn't a question. 8 BY MR. KANE: 9 Q. I thought it might be interesting for you 10 to know. 11 So let's try to kind of bear this out a 12 little bit. Let's look at your chart again on 68. 13 So if you had a patient that went from a 14 Schirmer score of 7 to 8, let's say. All right? 15 A. Yes. 16 MR. MILLS: Objection. Form. 17 BY MR. KANE: 18 Q. Okay. They, in Sall Figure 2, would be a 19 3, Category 3 patient, correct? 20 A. Yes. 21 Q. And they would be a Category 3 patient at 22 7? 23 A. Yes. 24 Q. And they would be a Category 3 patient at 25 8?</p> |
| <p style="text-align: right;">Page 99</p> <p>1 test, on average as a means of these -- of data in 2 these population groups. 3 So, in other words, we can quibble over 4 whether they're going from 3 millimeters to, you 5 know, 3.5 millimeters. I don't care if it's 4 6 millimeters to 4.5 or 5 millimeters to 5.5. We're 7 still talking about small changes. That's the whole 8 point of this investigation. I wouldn't have done 9 this in the first place if Allergan had supplied the 10 primary data, but they didn't. 11 BY MR. KANE: 12 Q. And, Doctor, you've said that multiple 13 times. You understand that Mylan asked for that 14 data from the patent office, don't you? 15 MR. MILLS: Objection. Foundation. 16 Argumentative. 17 THE WITNESS: I understand that I 18 requested it from WSGR counsel. And I'm not privy 19 to the conversations between them and opposing 20 counsel or the -- or the PTAB. 21 BY MR. KANE: 22 Q. Okay. 23 A. So I don't know exactly who did what or 24 who said what. What I know is that I asked for the 25 data and we didn't get it.</p> | <p style="text-align: right;">Page 101</p> <p>1 A. Yes. 2 Q. And they would be a Category 3 patient at 3 9? 4 A. Yes. 5 Q. And a Category 3 patient at 10? 6 A. Yes. 7 Q. So they could actually have a 2- or 8 3-millimeter increase in their Schirmer wetting 9 score, and they would still be the same 10 categorized -- have the same categorized Schirmer 11 score, right? 12 A. Unfortunately, that is correct. That is 13 the way they, unfortunately, decided to set this up. 14 Q. Okay. 15 A. I think it's important to make a 16 distinction between individual patients and large 17 groups of patients. 18 Obviously in a large group of patients, 19 the mean is going to be more -- if you do this 20 categorization on a single patient, you're going to 21 have a large disconnect between the actual values in 22 millimeters and the categories. If you're looking 23 at means of large numbers of patients, that will 24 tend to decrease the lack of correlation between the 25 categorized and the raw Schirmer's, although it's</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 102</p> <p>1 still an issue.</p> <p>2 Q. Did you attempt to quantify the impact on</p> <p>3 individual patients -- on the fact that this was</p> <p>4 done on a means of patients in this case?</p> <p>5 A. I'm not sure I understand the question.</p> <p>6 Q. Well, I understood what you were trying to</p> <p>7 say, that if you look at means of large numbers of</p> <p>8 patients, you tend to decrease the lack of</p> <p>9 correlation, right?</p> <p>10 A. In general, yes.</p> <p>11 Q. Okay. What impact did the number of</p> <p>12 patients in this study have on that lack of</p> <p>13 correlation?</p> <p>14 MR. MILLS: Objection. Form.</p> <p>15 THE WITNESS: Yeah, I don't know of a</p> <p>16 way -- the method that I would be aware of to</p> <p>17 determine that would be to compare the actual raw</p> <p>18 data for individual patients with the actual means.</p> <p>19 And to do that data analysis, it could be done if</p> <p>20 you had each individual patient's data, both raw and</p> <p>21 categorized.</p> <p>22 BY MR. KANE:</p> <p>23 Q. Okay. So you can't do it based on the</p> <p>24 data in Sall Figure 2?</p> <p>25 A. Unfortunately, no.</p> | <p style="text-align: right;">Page 104</p> <p>1 Schirmer testing. And in my experience, the</p> <p>2 variability is even worse with the Schirmer's with</p> <p>3 anesthesia because, if you think about it, when you</p> <p>4 put that eye drop in, it's hard to get all of that</p> <p>5 anesthetic eye drop out. The anesthetic eye drop</p> <p>6 itself sometimes causes some reflex tearing because</p> <p>7 it stings.</p> <p>8 And so that's why I've been careful all</p> <p>9 along to say to a first approximation, Schirmer's</p> <p>10 with anesthesia reflects basal tearing because it's</p> <p>11 an imperfect test. And in my experience, it's more</p> <p>12 variable than the Schirmer's without. Because if</p> <p>13 you've got that eye drop left over in the eye,</p> <p>14 that's going to give you a few millimeters right</p> <p>15 there. You know, if you've got reflexive tearing</p> <p>16 because the patient's getting stinging from the</p> <p>17 aesthetic, that's going to potentially give you more</p> <p>18 millimeters there. Those can vary from day to day,</p> <p>19 you know.</p> <p>20 It's -- it's -- so, you know, it's an</p> <p>21 imperfect test as it is, and you then put categories</p> <p>22 in and it makes it even more difficult to</p> <p>23 understand.</p> <p>24 BY MR. KANE:</p> <p>25 Q. You stated paragraph -- at the bottom of</p> |
| <p style="text-align: right;">Page 103</p> <p>1 Q. Okay. And so you can't do it with respect</p> <p>2 to your putative conversions that you've attempted</p> <p>3 to infer differences here?</p> <p>4 MR. MILLS: Objection. Form.</p> <p>5 THE WITNESS: Well, you -- I'm not trying</p> <p>6 to oversell this. I'm saying that this is an</p> <p>7 attempt to determine if the changes are small or</p> <p>8 large. And so I'm not trying to make any, you know,</p> <p>9 much more precise statement than that. But I think</p> <p>10 that this is useful in determining whether these are</p> <p>11 small or large differences on these mean</p> <p>12 populations. And in the absence of more fundamental</p> <p>13 data, it's hard to get more specific than that.</p> <p>14 But I would say that the largest increase</p> <p>15 you can have and still remain within a category, the</p> <p>16 boundary condition, in this range is 3 millimeters.</p> <p>17 So, you know, you can't have a</p> <p>18 4-millimeter change that doesn't result in a change</p> <p>19 in category. And 3 millimeters or less, in my mind</p> <p>20 as a clinician, is a small difference.</p> <p>21 Especially -- you know, Dr. Sheppard</p> <p>22 actually admitted this to -- the variability of</p> <p>23 Schirmer testing. And this was also brought out in</p> <p>24 the 1994 text, Smolin text, S-M-O-L-I-N, that I</p> <p>25 cited talking about the known variability of</p> | <p style="text-align: right;">Page 105</p> <p>1 68, for instance, you say a change in categorized</p> <p>2 score of approximately .25 would equate to</p> <p>3 1 millimeter.</p> <p>4 Do you see that?</p> <p>5 A. Correct.</p> <p>6 Q. And how --</p> <p>7 A. Well, no, it says 1.6 actually. Sorry.</p> <p>8 The whole sentence says: "A change in</p> <p>9 categorized score of approximately 0.40 would be</p> <p>10 8/5ths of the 0.25 required to increase</p> <p>11 1 millimeter, or 1.6 millimeter." That's what it</p> <p>12 says.</p> <p>13 Q. I was asking about the next section.</p> <p>14 A. I'm sorry. The next sentence says: "And</p> <p>15 a change in categorized score of approximately 0.25</p> <p>16 would equate to 1 millimeter."</p> <p>17 Again, I'm not being literal here. I'm</p> <p>18 just trying to get an idea of the magnitude of the</p> <p>19 change in the population.</p> <p>20 Q. But so we're clear on this. An individual</p> <p>21 patient can't get a change in categorized score of</p> <p>22 .25, right?</p> <p>23 A. Strictly speaking, no.</p> <p>24 Q. And you didn't do any analysis to</p> <p>25 determine what a change in average score on this</p> |

| | |
|--|---|
| <p style="text-align: right;">Page 106</p> <p>1 patient population of .025 would mean, correct?</p> <p>2 MR. MILLS: Objection. Form.</p> <p>3 THE WITNESS: I disagree. I did the</p> <p>4 best -- you seem to be criticizing or quibbling with</p> <p>5 me for doing the best I can with the limited data</p> <p>6 set to try to put these into clinical context, and I</p> <p>7 resent that. I don't think it's appropriate.</p> <p>8 If I had more data, I would have done a</p> <p>9 more complex analysis, but those data were not</p> <p>10 provided by whomever.</p> <p>11 So, in my experience, the -- the best that</p> <p>12 we can infer from this data set is that, on average,</p> <p>13 a change of .25 in categorized Schirmer score in a</p> <p>14 population, on average, would equate to 1 millimeter</p> <p>15 on average approximately.</p> <p>16 You know what? If we got the raw data and</p> <p>17 we did the analysis on the individual patients,</p> <p>18 maybe it's not 1 millimeter. Maybe it's a half a</p> <p>19 millimeter. Maybe it's 2 millimeters. It's not</p> <p>20 8 millimeters. It's not 5 millimeters. It's hard</p> <p>21 to see how it would even be 3 millimeters.</p> <p>22 BY MR. KANE:</p> <p>23 Q. But you didn't do that analysis because</p> <p>24 you can't do the analysis?</p> <p>25 A. Well, you're blaming me for the lack of</p> | <p style="text-align: right;">Page 108</p> <p>1 Do you see that?</p> <p>2 A. I do.</p> <p>3 Q. And where did you get those numbers?</p> <p>4 A. That was from Sall, I believe. Look at</p> <p>5 the -- let's see. Table -- let's see. That's</p> <p>6 actually in page 635 under "Schirmer tear test</p> <p>7 reporting baseline."</p> <p>8 Q. Okay. And then what about the 2. -- if</p> <p>9 you go to Month 3, baseline plus .09? So that is</p> <p>10 just an addition?</p> <p>11 A. Yes.</p> <p>12 Q. Based on Dr. Bloch's measurements?</p> <p>13 A. Yes.</p> <p>14 Q. And then Month 6, baseline plus 0.39, was</p> <p>15 an addition based on Dr. Bloch's measurements?</p> <p>16 A. Correct. I mean, obviously, I looked at</p> <p>17 the figure to verify that there was not a gross</p> <p>18 error, but yes.</p> <p>19 Q. If you want to go back, Dr. Calman, and</p> <p>20 look at paragraph 77 of Dr. Amiji's report.</p> <p>21 A. 77?</p> <p>22 Q. Yes. Dr. Amiji.</p> <p>23 THE WITNESS: And I note that the time now</p> <p>24 is 12:02.</p> <p>25 MR. KANE: Do you want to take a lunch</p> |
| <p style="text-align: right;">Page 107</p> <p>1 available data to do a more full analysis, and I</p> <p>2 don't think that's fair.</p> <p>3 Q. Okay. Would you feel comfortable standing</p> <p>4 up and presenting this analysis at a medical</p> <p>5 conference?</p> <p>6 A. If I had to present this data at a medical</p> <p>7 conference, I would be deeply apologetic at the fact</p> <p>8 that whoever was providing the data to me had given</p> <p>9 me an incomplete data set.</p> <p>10 And if for some reason I were presenting</p> <p>11 this -- let's say I was presenting some publication</p> <p>12 from a foreign country where I couldn't get any</p> <p>13 underlying data from the study participants. And I</p> <p>14 said, "This is the best I can do to translate this</p> <p>15 into raw Schirmer scores which you and I use in</p> <p>16 clinical practice. Please understand the</p> <p>17 limitations of this. This is not meant to be a</p> <p>18 literal conversion, and it has its limitations</p> <p>19 because we don't have the raw data set." But, yeah,</p> <p>20 I'm comfortable saying that what study shows is</p> <p>21 small changes in Schirmer scores.</p> <p>22 Q. If we look at the paragraph 69, there's --</p> <p>23 again, there's a lot of values in here. For</p> <p>24 instance, Schirmer score under the "Baseline" column</p> <p>25 on the top section, 1.94 to 2.11.</p> | <p style="text-align: right;">Page 109</p> <p>1 break?</p> <p>2 THE WITNESS: I don't know if lunch has</p> <p>3 been brought in. I just note the time.</p> <p>4 MR. MILLS: I expect that it has.</p> <p>5 BY MR. KANE:</p> <p>6 Q. You recall earlier we looked at a sentence</p> <p>7 in here where Dr. Amiji concluded that 0.05 percent</p> <p>8 treatment has an average change in Schirmer score of</p> <p>9 more than one standard deviation higher (better)</p> <p>10 than the CsA 0.1 percent treatment.</p> <p>11 Do you recall that?</p> <p>12 A. I also recall that I wasn't sure exactly</p> <p>13 where he got that number.</p> <p>14 Q. Okay.</p> <p>15 A. And I would also point out, I think that</p> <p>16 probably everybody knows that one standard deviation</p> <p>17 does not imply statistical significance.</p> <p>18 Q. And --</p> <p>19 A. He did write that.</p> <p>20 Q. He did write that. And despite his</p> <p>21 statement to that effect, you look at the Sall</p> <p>22 Figure 2 and conclude, based on your analysis, that</p> <p>23 it is not a clinically significant change, correct?</p> <p>24 A. Well, hang on a second. You're conflating</p> <p>25 a bunch of things here.</p> |

| | |
|--|---|
| <p style="text-align: right;">Page 110</p> <p>1 Where's the statement that you're talking</p> <p>2 about with the one standard deviation?</p> <p>3 Q. Bottom of page 33 in paragraph 77.</p> <p>4 A. All right. Let me just read your question</p> <p>5 here.</p> <p>6 Well, so, first of all, I think you're</p> <p>7 taking that one sentence out of context.</p> <p>8 Allergan itself did the analysis and did</p> <p>9 not report a statistically significant difference</p> <p>10 between .05 and .1 at any time point with regard to</p> <p>11 any of the types of Schirmer testing.</p> <p>12 And Dr. Bloch, in his own analysis, did</p> <p>13 not find such a statistically difference either. So</p> <p>14 one standard deviation is sort of, you know, neither</p> <p>15 here nor there. And even if you just take the raw</p> <p>16 values with all the caveats that I have stated</p> <p>17 repeatedly I attempted to do in the absence of the</p> <p>18 raw data, you come up with a difference, on average,</p> <p>19 of a 1-millimeter increase for the .1 percent and</p> <p>20 1.6-millimeter for the .05 percent at Month 6.</p> <p>21 These are very small increases.</p> <p>22 And as a cross-check on this, I note that</p> <p>23 although we don't have the complete raw data set,</p> <p>24 Dr. -- the FDA did indicate only 15 percent of the</p> <p>25 .05 percent CSA group achieved a 10-millimeter</p> | <p style="text-align: right;">Page 112</p> <p>1 --o0o--</p> <p>2</p> <p>3</p> <p>4</p> <p>5</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p> |
| <p style="text-align: right;">Page 111</p> <p>1 increase.</p> <p>2 So obviously there are some patients who</p> <p>3 have more of an increase than others. There may be</p> <p>4 even some who had a decrease. But, on average,</p> <p>5 these are small increases with a small difference in</p> <p>6 the means between them. 1 millimeter or 1.6</p> <p>7 millimeter. I can't even get a reproducible</p> <p>8 Schirmer test from day to day that's within 1</p> <p>9 millimeter, and Dr. Sheppard admitted as much in his</p> <p>10 deposition.</p> <p>11 Q. And so -- and the 1 millimeter and the</p> <p>12 1.6 millimeter are based on your analysis of these</p> <p>13 inferred values, correct?</p> <p>14 A. Correct. And if you think about it,</p> <p>15 again, as I said, if it were more than 3-millimeter</p> <p>16 difference on average, then on average you'd have at</p> <p>17 least one full category change.</p> <p>18 So, you know, we can quibble over whether</p> <p>19 it's really 1, or maybe it's 1 1/2, or maybe it's 2,</p> <p>20 but it sure isn't 7 or 10.</p> <p>21 MR. MILLS: Are we ready for lunch?</p> <p>22 MR. KANE: Let's see.</p> <p>23 Yeah. We can take lunch now.</p> <p>24 (Whereupon the luncheon recess was taken</p> <p>25 at 12:05 p.m.)</p> | <p style="text-align: right;">Page 113</p> <p>1 JULY 12, 2017 AFTERNOON SESSION 12:49 P.M.</p> <p>2 --o0o--</p> <p>3 BY MR. KANE:</p> <p>4 Q. Okay. Let's turn to paragraph 73 of your</p> <p>5 declaration, Dr. Calman.</p> <p>6 And the first sentence there refers to the</p> <p>7 Restasis label that we've discussed earlier,</p> <p>8 Exhibit 2008. And as we've seen, it mentions an</p> <p>9 increase in Schirmer wetting of 10 millimeters or</p> <p>10 greater.</p> <p>11 Do you recall that?</p> <p>12 A. I want to look and see if -- did you say</p> <p>13 2008?</p> <p>14 Q. Exhibit 2008, yes.</p> <p>15 A. Oh, okay.</p> <p>16 I do recall that.</p> <p>17 Q. And then the second sentence of paragraph</p> <p>18 73, you're stating that, in your view, a Schirmer</p> <p>19 tear test with anesthesia, increase of greater than</p> <p>20 10 millimeters, is clinically meaningful and</p> <p>21 material, right?</p> <p>22 A. Well, I didn't say without anesthesia or</p> <p>23 with anesthesia. But I would agree that, in</p> <p>24 general, an increase in Schirmer test of</p> <p>25 10 millimeters is clinically meaningful and material</p> |

| | |
|---|---|
| <p style="text-align: right;">Page 114</p> <p>1 in an individual patient, yes.</p> <p>2 Q. Okay. I mean, with respect to the FDA</p> <p>3 label where it says "STT," do you understand that to</p> <p>4 be with or without anesthesia?</p> <p>5 A. Let me go back. I believe that was on</p> <p>6 page 5.</p> <p>7 Q. Correct.</p> <p>8 A. It does not state.</p> <p>9 Q. Would it make a difference if it was with</p> <p>10 or without anesthesia?</p> <p>11 A. Well, theoretically, it might. I'm trying</p> <p>12 to envision a situation where all the -- you know,</p> <p>13 in theory, if it were all reflex only and you had a</p> <p>14 patient with very low basal Schirmer score and a</p> <p>15 theoretical drug increased only the reflexive</p> <p>16 aspects of tearing with all the caveats we discussed</p> <p>17 earlier regarding testing methodology and</p> <p>18 oversimplification, in that situation, the patient</p> <p>19 still might be symptomatic from dryness. But I</p> <p>20 think that would be rather unusual.</p> <p>21 So, you know, again, to a first</p> <p>22 approximation, in general, if you had an increase in</p> <p>23 Schirmer score of that magnitude, whether with or</p> <p>24 without anesthesia, it would likely correlate with</p> <p>25 material improvement of the patient's condition.</p> | <p style="text-align: right;">Page 116</p> <p>1 clear, I mean what I'm saying here is not that there</p> <p>2 is no individual piece of data that looks like</p> <p>3 there's a difference in favor of .05, you know, for</p> <p>4 that matter in favor of .1. But looking at my</p> <p>5 review of the declaration and the exhibits and</p> <p>6 thinking about that totality of data, I've seen no</p> <p>7 clinical evidence that, in general, that .05 works</p> <p>8 better or works differently.</p> <p>9 I think that is an important basis of my</p> <p>10 conclusions. I'm not sure I would agree that it</p> <p>11 underlies the totality of my conclusions.</p> <p>12 BY MR. KANE:</p> <p>13 Q. Okay. And at the end of paragraph 74, you</p> <p>14 cite: "There is, in fact, no evidence that the</p> <p>15 0.05 percent CsA formulation increased</p> <p>16 tear production, more than the 0.1 percent CsA</p> <p>17 formulation," correct?</p> <p>18 A. That's what I wrote.</p> <p>19 Q. And that's your understanding?</p> <p>20 A. Well, yeah, you know, again, taking into</p> <p>21 account all the other arguments in my declaration</p> <p>22 and the underlying data and other materials.</p> <p>23 Q. If there were evidence that the</p> <p>24 0.05 percent CsA formulation increased</p> <p>25 tear production more than 0.1 percent CsA</p> |
| <p style="text-align: right;">Page 115</p> <p>1 Q. Okay. And that's what you say in</p> <p>2 paragraph 73, is that it's generally clinically</p> <p>3 meaningful and material?</p> <p>4 A. In fewer words with less nuance, but yes.</p> <p>5 Q. All right. And then at the end of</p> <p>6 paragraph 73, you say -- and can read the whole</p> <p>7 paragraph, if you need to. But you say: "Based</p> <p>8 upon my review of those declarations, exhibits they</p> <p>9 rely upon, I have seen no clinical evidence that the</p> <p>10 0.5 percent formulation works better or works</p> <p>11 differently than the 0.1 percent" -- "0.05." I</p> <p>12 might have said that wrong. I keep saying that</p> <p>13 wrong. Let me start over.</p> <p>14 You say: "I have seen no clinical</p> <p>15 evidence that the 0.05 percent formulation works</p> <p>16 better or works differently than the 0.1 percent CsA</p> <p>17 formulation evaluated in Sall."</p> <p>18 Do you see that?</p> <p>19 A. I do see that.</p> <p>20 Q. And is that -- is it fair to say that that</p> <p>21 underlies your entire opinion that there are no</p> <p>22 unexpected results between the 0.05 percent</p> <p>23 formulation and the 0.1 percent formulation?</p> <p>24 MR. MILLS: Objection. Form.</p> <p>25 THE WITNESS: Well, first of all, to be</p> | <p style="text-align: right;">Page 117</p> <p>1 formulation, would that change your opinion?</p> <p>2 A. Well, it would depend. I mean, if you</p> <p>3 showed me that it increased tear production a little</p> <p>4 bit more, you know, I don't think that would change</p> <p>5 my overall conclusions.</p> <p>6 If you showed me that it increased it but</p> <p>7 it was -- the increase was not statistically</p> <p>8 significant, that probably would not change my</p> <p>9 opinion.</p> <p>10 If you showed me that it did increase it</p> <p>11 by a little bit but not an amount that I would</p> <p>12 consider clinically material, that would probably</p> <p>13 not change my opinion.</p> <p>14 If the increase were by a methodology that</p> <p>15 was flawed, that would probably not change my</p> <p>16 opinion.</p> <p>17 But if you came to me with a</p> <p>18 well-controlled study with good data that showed</p> <p>19 that, say, the mean, hypothetically, you know, the</p> <p>20 mean increase in Schirmer was 7 or 8 millimeters</p> <p>21 more than the .05, than the .1, and that that was</p> <p>22 statistically significant and that that was</p> <p>23 reproducible and that the study was well designed</p> <p>24 and well controlled, I would certainly have to give</p> <p>25 that some weight and rethink my conclusions.</p> |

| | |
|--|---|
| <p style="text-align: right;">Page 118</p> <p>1 But to my knowledge, such a hypothetical</p> <p>2 study does not exist.</p> <p>3 Q. Can you look back at 2008 again for me?</p> <p>4 A. So this is the label?</p> <p>5 Q. Yes. So there again it refers to STT</p> <p>6 increases of greater than 10 millimeters, correct?</p> <p>7 A. Yes.</p> <p>8 Q. And we've talked about that, that you view</p> <p>9 that as clinically meaningful and material, right?</p> <p>10 A. In that individual patient who gets the</p> <p>11 10-millimeter increase, yes.</p> <p>12 Q. And as the FDA describes the Phase 3</p> <p>13 studies, it says that 15 percent of the patient</p> <p>14 population achieve that score using the Restasis</p> <p>15 formulation, correct?</p> <p>16 A. Well, 15 percent of "a patient</p> <p>17 population," and we don't know what that patient</p> <p>18 population is and whether it's the same as the one</p> <p>19 in Sall. I can only go by what it says here.</p> <p>20 Q. Okay. But it's referring to -- well,</p> <p>21 okay.</p> <p>22 It's referring, though, to the randomized</p> <p>23 multicenter studies, correct?</p> <p>24 MR. MILLS: Objection. Form.</p> <p>25 THE WITNESS: So I have to say that the</p> | <p style="text-align: right;">Page 120</p> <p>1 Schirmer wetting score of 10-millimeter or greater,</p> <p>2 would that change your opinion?</p> <p>3 MR. MILLS: Objection. Form. Incomplete</p> <p>4 hypothetical.</p> <p>5 THE WITNESS: I'm not sure I understand</p> <p>6 the question. It is incomplete and there are other</p> <p>7 problems as well.</p> <p>8 Part of the problem is that you have to</p> <p>9 look at the totality of the study. If the study</p> <p>10 were designed at the outset to look specifically at</p> <p>11 this 10-millimeter increased parameter and that were</p> <p>12 not some retrospective relook at the data or</p> <p>13 reanalysis of the data, then I would give it more</p> <p>14 weight.</p> <p>15 If the increase in Schirmer score was</p> <p>16 superior and lots of other parameters that I would</p> <p>17 expect to be correlated with that were also</p> <p>18 superior, I would give it more weight.</p> <p>19 Frankly, if it affected more than</p> <p>20 15 percent of the patients, I would give it more</p> <p>21 weight because 15 percent is a pretty small number.</p> <p>22 So it really is very situation-specific.</p> <p>23 You know, the problem is that if you take</p> <p>24 a big data set and you do a reanalysis, you can --</p> <p>25 it would be an exaggeration to say that you can</p> |
| <p style="text-align: right;">Page 119</p> <p>1 reason I'm trying to -- you know, again, confining</p> <p>2 to this only what a POSA would have known at the</p> <p>3 time. But the way the label is worded, it does say:</p> <p>4 "Patients whose tear production is presumed to be</p> <p>5 suppressed due to ocular inflammation associated</p> <p>6 with KCS."</p> <p>7 So I guess my question is: Is this the</p> <p>8 whole study group or is it some subgroup? And I</p> <p>9 don't know from this document.</p> <p>10 So in some particular group or subgroup of</p> <p>11 patients, they're asserting that, you know,</p> <p>12 15 percent of them had this 10-millimeter response.</p> <p>13 And there's just not enough detail to go -- to</p> <p>14 understand it more thoroughly.</p> <p>15 BY MR. KANE:</p> <p>16 Q. And they also say that Restasis</p> <p>17 demonstrated statistically significant increases in</p> <p>18 Schirmer wetting scores.</p> <p>19 Do you see that?</p> <p>20 A. Where are we seeing that?</p> <p>21 Q. In the first sentence.</p> <p>22 A. Versus vehicle at six months.</p> <p>23 Q. Versus vehicle, right.</p> <p>24 And so if there's a patient population</p> <p>25 that has a statistically significant increase in</p> | <p style="text-align: right;">Page 121</p> <p>1 prove anything you want, but you could prove a lot</p> <p>2 of things that might turn out not to be true if the</p> <p>3 study were repeated.</p> <p>4 Again, it comes back to this notion of the</p> <p>5 Bonferroni correction, which I didn't explain in</p> <p>6 detail, but it's an attempt to say that a P of less</p> <p>7 than .05 is a useful cutoff, but if you measure a</p> <p>8 lot of measure -- a lot of parameters, some of them</p> <p>9 are going to be positive at a P .05 level by random</p> <p>10 chance alone. In fact, about 1 out of 20.</p> <p>11 So what these corrections -- and there are</p> <p>12 a variety of them. Bonferroni, I think, was the</p> <p>13 first. What they do is they, at the simplest level,</p> <p>14 you simply divide the .05 threshold by the number of</p> <p>15 parameters you're testing.</p> <p>16 So if I'm doing 20 blood tests on you, I</p> <p>17 would consider something to be -- a blood test may</p> <p>18 be not the best criterion. If I'm doing 20 -- if</p> <p>19 I'm evaluating a patient for 20 different parameters</p> <p>20 and comparing two subgroups, two treatments in two</p> <p>21 different population subgroups, on average, one of</p> <p>22 them is going to appear to be positive at a .05</p> <p>23 level. So what I should do is divide that .05 by</p> <p>24 some factor.</p> <p>25 Well, Bonferroni, if I recall correctly,</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 122</p> <p>1 is to just divide it by the 20, which is the number 2 of parameters. 3 So, in that situation, it would have to be 4 significant P less than .0025, which is 1/20th of 5 .05. 6 And there are others because that's 7 thought to be somewhat too conservative. 8 But my point remains that you know, if 9 you're doing these sort of post hoc analyses, you 10 have to either very good collateral evidence of the 11 validity of the conclusion or reproducibility when 12 you say, "Oh, well, it looks like we did a 13 reanalysis of our study and this popped out." Now 14 that is a study where that is the thing we're going 15 to measure. We're going to decide that at the 16 outset, and that's our treatment goal. 17 Or the stats have to show just an 18 extremely strong correlation or some kind of 19 combination of those. 20 So I can't just give you a one size fits 21 all answer to that question. 22 BY MR. KANE: 23 Q. Okay. Well, Restasis got approved by the 24 FDA, right? 25 A. Correct.</p> | <p style="text-align: right;">Page 124</p> <p>1 approximately 15 percent of the -- of the patients 2 versus 5 percent of the vehicle-treated patients? 3 MR. MILLS: Objection. Form. 4 THE WITNESS: That's not exactly what it 5 says, but it's close. And it's close to my 6 understanding. 7 BY MR. KANE: 8 Q. Okay. And you're not taking an issue with 9 what the FDA did, right? 10 A. Well, I think in order to answer that 11 question, I would have to be provided with more -- 12 more information, including the NDA and the FDA 13 correspondence, because I -- don't think they're 14 infallible. 15 Q. Okay. I think we talked about this 16 earlier. You didn't look at any of the public FDA 17 files in connection with the IPR declaration that 18 you've submitted here, correct? 19 A. Not in connection with the IPR 20 declaration, no. 21 Q. Okay. I want to turn to paragraph 78 of 22 your declaration, Dr. Calman. And this is a 23 discussion of Dr. Attar's presentation of PK data. 24 Do you see that? 25 A. Yes.</p> |
| <p style="text-align: right;">Page 123</p> <p>1 Q. And this is how they described the results 2 on the label, correct? 3 A. Well, I'm sure there's another document 4 that has a much more detailed description because 5 that's the way the FDA operates. But there is this 6 paragraph on the label. 7 Q. And so -- and you understand that -- you 8 agree the FDA has expertise in approving drugs? 9 A. Well, that's a pretty broad blanket 10 statement. One would hope so. I don't think they 11 do a perfect job. 12 Q. Okay. And you understand the FDA has 13 statisticians who analyze clinical results to 14 determine whether or not the trials have shown 15 safety in efficacy of the drugs? 16 A. I do understand that they employ 17 statisticians. 18 Q. Have you ever worked with the 19 statisticians at the FDA? 20 A. Not that I recall. 21 Q. Okay. And so is it your understanding 22 that the -- that the FDA concluded that Restasis had 23 demonstrated statistically significant increases in 24 Schirmer wetting of greater than 10 millimeters 25 versus vehicle and that that effect had been seen in</p> | <p style="text-align: right;">Page 125</p> <p>1 Q. And you see there you've got some bold 2 text that says -- well, the sentence says: 3 "However, this presentation is misleading, because 4 each formulation delivered CsA to the corneal 5 conjunctiva well above" -- I think I said that wrong 6 -- "well above the threshold required for 7 therapeutic efficacy." 8 Do you see that? 9 A. I see that. 10 Q. Okay. And then if you turn to -- well, 11 okay. So let's -- in that context, let's look at a 12 document we previously marked as Exhibit 1058. 13 Do you recall reviewing this document as 14 part of your work in this matter, Dr. Calman? 15 A. Yes. 16 Q. Okay. And you'd agree that this document 17 is relating to the use of cyclosporin as an 18 immunosuppressant in organ transplantation? 19 A. Generally speaking -- generally speaking, 20 that's true. 21 Q. Okay. And you understand that these organ 22 transplant patients are not generally treated with 23 topical cyclosporin? 24 A. That is my understanding. 25 Q. Okay. And the paper here is describing</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 126</p> <p>1 therapeutic ranges of CsA in the blood streams of 2 patients? 3 A. Yes. 4 Q. And, in fact, if you look -- looks like -- 5 excuse me. Table 2 on page 651. 6 A. Yes. 7 Q. You see there that it's titled 8 "Therapeutic ranges for cyclosporin stratified 9 according to transplanted organ, immunosuppressive 10 regime, induction/maintenance therapy and 11 immunoassay technique." 12 Do you see that? 13 A. I do. 14 Q. And you see there they've got then for 15 kidney triple therapy, heart triple therapy, liver 16 triple therapy, and liver double therapy categories, 17 right? 18 A. Yes. 19 Q. And for the different therapies, there are 20 actually different therapeutic ranges shown, aren't 21 there? 22 A. Somewhat. 23 Q. Okay. 24 A. They're not dramatically different. 25 Q. But they are different and they are</p> | <p style="text-align: right;">Page 128</p> <p>1 A. Correct. 2 Q. And you cite pages 652 to 653? 3 A. Well, I believe there may be some other 4 pages that have relevant data too. For example -- 5 well, yeah, 652 and 653, yeah. There may be issues 6 on some other pages, but, yeah, that was what I was 7 primarily looking at. 8 Q. And I believe it's the section at the top 9 of the left-hand column on page 653 is where you 10 have a quote. 11 A. Yeah. 12 Q. Well, actually, it starts at 652. 13 And you state there that the intraocular 14 concentrations of 50 to 300 nanograms per ML were 15 large enough to control uveitis? 16 A. That's what it says. 17 Q. And where do you -- where exactly did you 18 find that in there in the paper, Doctor? 19 A. Top of page 653. 20 Q. It says -- the sentence that -- let me 21 just read the sentence. It says: "The therapeutic 22 range for organ transplantation is 200 to 600 23 nanograms per milliliter serum, but intraocular 24 level speculated to be needed for control of uveitis 25 is 50 to 300 nanograms per ML."</p> |
| <p style="text-align: right;">Page 127</p> <p>1 measured in the bloodstream? 2 A. They are somewhat different, and they are 3 measured in the bloodstream. 4 Q. Okay. And they're not being measured in 5 any targeted issues, are they? 6 A. The data that we've talked about so far 7 are not. I'm not sure if there are any -- some of 8 the references stated in here may refer to targeted 9 issue. But this particular one was looking at blood 10 levels. 11 Q. Okay. Hand you a document previously 12 marked as Exhibit 1011, Dr. Calman. 13 A. Correct. 14 Q. Are you familiar with this document? 15 A. Yes. 16 Q. This is an article by Dr. Kaswan? 17 A. Yes. 18 Q. And if we look at paragraph 79, this is 19 the -- one of the references that you cite -- 20 A. Correct. 21 Q. -- as being -- well, cite for the 22 proposition that the values shown in the Attar PK 23 study are higher than those that had been identified 24 in the literature prior to September 15, 2003, as 25 therapeutically effective, right?</p> | <p style="text-align: right;">Page 129</p> <p>1 Is that the sentence that we're looking 2 at? 3 A. I see that, yes. 4 Q. And that's what you were referring to 5 where this quote comes from in paragraph 69? 6 A. Yes. 7 Q. And it says there that -- well, first of 8 all, it's talking about intraocular level. 9 What do you understand that to be? 10 A. Well, uveitis is an inflammation of the -- 11 typically of the iris and ciliary -- sometimes 12 ciliary bodies, C-I-L-I-A-R-Y. Sometimes posterior 13 structures as well but usually the iris. 14 And so typically the target tissue would 15 be the aqueous humour, which is why that specifies 16 nanograms per ML rather than nanograms per gram 17 because the aqueous humour is liquid. 18 Q. And what is the aqueous humour? Where is 19 that located? 20 A. Well, the aqueous humour is located 21 posterior to the cornea. It's the fluid that fills 22 the front part of the eye. 23 Q. So it's a fluid inside the eye? 24 A. Yes. 25 Q. Okay. And it says there that it's</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 130</p> <p>1 speculated that the level to control uveitis is 50 2 to 350 milligrams per ML in the aqueous humour. 3 Is that how you're interpreting that? 4 A. I see that. 5 Q. And that's how you interpret that to mean? 6 A. It says what it says. 7 Q. Okay. And then there's a -- and you said, 8 I believe, uveitis is a condition affecting the 9 iris? 10 A. Well, it's a condition -- so, strictly 11 speaking, uveitis is inflammation of the uvea, 12 U-V-E-A. And the uveal tract, U-V-E-A-L, is 13 comprised of the iris; the ciliary body, 14 C-I-L-I-A-R-Y; and the choroid, C-H-O-R-O-I-D. So, 15 strictly speaking, uveitis can be inflammation of 16 any or all of those layers. 17 Typically, it's if affecting the posterior 18 portion of the eye, we would not typically actually 19 use the term "uveitis." We would call it 20 choroiditis, C-H-O-R-O-I-D-I-T-I-S, or 21 chorioretinitis, C-H-O-R-I-O-R-E-T-I-N-I-T-I-S. 22 Or if all of the uveal tract is involved, 23 we would call it panuveitis. 24 So typically when people use the term 25 "uveitis" colloquially, they mean either iritis or</p> | <p style="text-align: right;">Page 132</p> <p>1 you've just mentioned, correct? 2 A. I disagree. The aqueous humour is a 3 tissue. 4 Q. Is the aqueous humour where the 5 inflammation is? 6 A. Well, the aqueous humor is where the 7 inflammation is manifest, and it is the tissue that 8 bathes the iris and ciliary body. And, in fact, 9 it's, in part, secreted by the ciliary body. 10 But in terms -- I think I can anticipate 11 what I think you're asking, is they didn't state a 12 level in the iris or the choroid or the ciliary 13 body. 14 Q. Right. Thank you. You anticipated my 15 question. 16 And we -- it cites to -- has a Note 6 17 there. 18 Do you see that? 19 A. I do. 20 Q. And that is Nussenblatt? 21 A. Nussenblatt, et al., Archives of 22 Ophthalmology. 23 Q. Okay. Now we are going to have to mark 24 one. This will be 2077. 25</p> |
| <p style="text-align: right;">Page 131</p> <p>1 iridocyclitis, which is I-R-I-D-O-C-Y-C-L-I-T-I-S, 2 which means inflammation of the iris and ciliary 3 body. 4 So this is an inflammation inside the eye 5 where -- usually manifested by inflammation, 6 including white blood cells and protein exudation, 7 E-X-U-D-A-T-I-O-N, in the anterior chamber in the 8 aqueous humour. 9 And so the treatment typically requires 10 relatively heavy doses of anti-inflammatory topical 11 drugs, sometimes supplemented with systemic drugs. 12 It's typically a pretty heavy-duty inflammation. 13 It's a semi-ocular emergency or urgency. 14 Q. And Exhibit 1011, is there any mention -- 15 A. 1011 is which one? 16 Q. The Kaswan paper. 17 A. Okay. 18 Q. The sentence that we were just looking at. 19 So it's talking -- that, as we just discussed, is 20 talking about the levels of cyclosporin -- 21 speculated levels of cyclosporin in the intraocular 22 fluid, correct? 23 A. In the aqueous humour. 24 Q. Okay. And it's not talking about the 25 levels of cyclosporin in any of the tissues that</p> | <p style="text-align: right;">Page 133</p> <p>1 (Whereupon Exhibit 2077 was marked for 2 identification.) 3 MR. MILLS: So my objection is that 4 Exhibit 1011 was submitted with Dr. Amiji's 5 declaration with the petitioners in these IPRs and 6 that Allergan's submission of Exhibit 2077 at this 7 point in the proceeding after it already has 8 submitted its patent in response and its responsive 9 declarations is belated. 10 BY MR. KANE: 11 Q. Dr. Calman, did -- if you look back to 12 Kaswan 6 there. This refers to an article by 13 Nussenblatt, Dinning, Fujikawa in the A-R-C-H. I'm 14 not sure what that stands for, A-R-C-H. 15 A. Archives of Ophthalmology. 16 Q. A-R-C-H-O-P-H-T-H-A-L-M-O-L. 103:1559, 17 1995. 18 Do you see that? 19 A. You're asking me? 20 Q. I'm asking if you see that on 6, yes. 21 A. You're asking me if I see the citation, 22 Archives of Ophthalmology, or are you asking if I 23 see it on this -- or on Kaswan? 24 Q. I'm asking first if you see it on Kaswan. 25 A. Yes.</p> |

| | |
|---|---|
| <p style="text-align: right;">Page 134</p> <p>1 Q. Okay. This is -- does what I marked as 2 Exhibit 2077 appear to be that article? 3 A. Yes. 4 Q. Is this an article you reviewed? 5 A. I am sure I read it when it first -- well, 6 actually, it was 1985, so I probably did not read it 7 when it first came out, and I have not read it 8 recently. 9 So if we're going to talk about it, I'd 10 like a few minutes to read it. 11 Q. Okay. Why don't you do that. 12 (Witness reviewing document.) 13 THE WITNESS: I've read it. Thank you. 14 BY MR. KANE: 15 Q. Having read the paper, does it refresh 16 your recollection as to having previously read this 17 paper? 18 A. I don't think I read this paper prior to 19 this. 20 Q. Okay. If we turn to page 1562, the middle 21 column, the first sentence there says: "As we have 22 noted, topical therapy" -- 23 A. Wait. Where are we? 24 Q. Middle column, about halfway down. "As we 25 have noted" in that paragraph.</p> | <p style="text-align: right;">Page 136</p> <p>1 they found in Table 1 was that the 80-microgram 2 injection was not effective and that the 3 500-milligram, which I think is probably a 4 microgram, injection was effective. 5 In fact, let's go back to materials and 6 methods. It would almost be impossible for it to be 7 milligrams. 8 In any case, with the lower dosage as seen 9 in Table 2 -- and, again, it may be a typo -- here 10 it says 800 micrograms. But, in any case, with the 11 higher dosage of intravitreal injection, they were 12 seeing cyclosporin levels -- mean cyclosporin levels 13 between 160 and 580 nanograms per gram, depending on 14 the time after injection. And with lower 15 concentration of cyclosporin intravitreal injection, 16 they were seeing intravitreal -- intraocular levels 17 of 30 to 80 nanograms per gram. 18 And so, again, the one with the higher 19 level worked with levels in tissue, in vitreous 20 tissue, in the 160 to 580 range, which is roughly 21 comparable to all these others ranges we've been 22 discussing with regard to serum levels. And the 23 lower dose, in the 30 to 80 range, was relatively 24 ineffective for EAU, which stands for experimental 25 autoimmune uveitis, which is a model of severe</p> |
| <p style="text-align: right;">Page 135</p> <p>1 A. Yeah. 2 Q. "As we have noted, topical therapy seemed 3 predictably effective only if serum cyclosporin 4 levels entered what is considered the therapeutic 5 range of 50 to 300 nanograms per ML." 6 Do you see that? 7 A. I do see that. 8 Q. And when it says "serum" there, you 9 understand that means levels in the blood? 10 A. Yes. 11 Q. Okay. And I believe that's the only 12 reference in this paper to 50 to 300 nanograms per 13 ML. 14 A. Well, let me look and see. But there's 15 more to the paper than that, too, that's relevant 16 here. 17 Yeah, that is a reference to 50 to 300. 18 But also relevant is the fact that when they 19 injected the -- within the intravitreal injection 20 group, as seen on Table 2 on page 1561, you can see 21 that there -- they looked at the -- the level -- the 22 intraocular concentration of cyclosporin after a 23 single injection or after an injection. 24 And in Table 1, they looked at the 25 efficacy of the intravitreal injection. And what</p> | <p style="text-align: right;">Page 137</p> <p>1 chorioretinitis in rats. Again, another pretty 2 big-time, high-powered anti-inflammatory disease. 3 So reading this, that's my take on this, 4 that we're -- again, we can quibble is it 50 to 300 5 or is it 160 to 580 or is it 100 to 400. All of 6 these are in the same ballpark. 7 Q. Okay. So -- 8 A. You know, one of the conclusions we 9 haven't talked about in this paper was that some of 10 the rats got better because rats being small, the 11 dosage administered topically actually resulted in 12 high blood levels of cyclosporin. That's one of the 13 conclusions of the paper. 14 Q. Okay. So a couple of things. 15 If we look at Table 2, the results there 16 are being reported in milligrams per milliliter. 17 Do you see that? 18 A. Yeah. I think that's wrong too. There's 19 just no way you can get those kinds of levels. 20 Q. Okay. 21 A. It wouldn't dissolve. We know that 22 cyclosporin has very low solubility in aqueous 23 solution, and the vitreous humour is an aqueous 24 solution with some collagen strands. It's not an 25 oily tissue. There's just no way.</p> |

| | |
|--|---|
| <p style="text-align: right;">Page 138</p> <p>1 And I'm just seeing lots of typos in this 2 paper. You know, is it 500? So we've got 3 800 micrograms for the intravitreal injection which 4 is plausible. But then in "Materials and Methods," 5 it says 500 milligrams, which is not plausible. You 6 couldn't get that much to dissolve. There's no way 7 you're going to get 500 milligrams of cyclosporin 8 into a rat eye unless it's a hunk of insoluble, you 9 know, solid.</p> <p>10 So I think these are typos.</p> <p>11 Q. I think in your answer earlier, though, 12 you had mentioned -- you used the term "showing 13 nanograms per gram" in Table 2?</p> <p>14 A. Well, it would be nanograms per ML. Gram 15 is the usual way you measure it in a solid tissue.</p> <p>16 And a milliliter, which a milliliter of 17 water weighs exactly 1 gram. A milliliter is how 18 you measure it in blood or aqueous.</p> <p>19 Vitreous is typically kind of a gel, so it 20 sort of has properties in between a liquid and a 21 solid. So you could actually plausibly measure in 22 vitreous either in nanograms per ML or nanograms per 23 gram. The difference is essentially immaterial.</p> <p>24 The "milligrams per ML" is clearly a typo.</p> <p>25 Q. Okay. All right.</p> | <p style="text-align: right;">Page 140</p> <p>1 more than a gram but not a lot. So it's not a 2 material difference.</p> <p>3 My interpretation of this is what they're 4 actually measuring here is nanograms per ML.</p> <p>5 Q. Right. But it's not nanograms per gram?</p> <p>6 A. I just went through that. It could be 7 nanograms per gram. It's essentially the same. It 8 may be off by a few percent. You're asking me -- 9 essentially the question you're asking me is how 10 much does a milliliter of rat vitreous weigh. Well, 11 it probably weighs a little bit more than a gram.</p> <p>12 Q. Well, would you express a concentration of 13 cyclosporin in, say, the iris in nanograms per 14 milliliter?</p> <p>15 A. Well, again, as I said previously, 16 typically in a solid tissue, you'd measure in 17 nanograms per gram.</p> <p>18 In a liquid tissue, like blood or aqueous 19 humour, you'd measure nanograms per ML.</p> <p>20 In a vitreous, it's kind of a half solid, 21 half liquid. It's a gel. So you could measure it 22 either way. You could weigh the tissue or you could 23 measure its volume either way.</p> <p>24 The results are not going to be very 25 different because a milliliter of a liquid or</p> |
| <p style="text-align: right;">Page 139</p> <p>1 A. There's no way physically possible to have 2 a 580 milligrams per ML concentration of cyclosporin 3 in vitreous. It just cannot physically be done. We 4 know it's a very insoluble compound in aqueous 5 solution.</p> <p>6 Q. But -- and based on your previous answer, 7 Table 2, then, is reporting the concentrations in 8 the aqueous rather than a concentration in a solid?</p> <p>9 A. Well, no. I think you're conflating 10 aqueous as in aqueous humour and aqueous as in not 11 oily.</p> <p>12 So, anatomically, you know, there's the 13 aqueous humour in the front part of the eye. 14 There's the vitreous humour in the back part of the 15 eye. They do communicate. The vitreous has a 16 larger volume, and it is a more gelatinous, like a 17 gel, at least in a young individual or animal 18 because it's got a lot of collagen fibers, it's got 19 a lot of high molecular weight dissolved molecules. 20 But, you know, it can be measured either in 21 milliliters or grams.</p> <p>22 The -- you know, because a gram of water 23 weighs -- a milliliter of water weighs a gram, a 24 milliliter of a -- you know, an animal liquid or 25 gelatinous tissue weighs, you know, maybe a little</p> | <p style="text-align: right;">Page 141</p> <p>1 gelatinous animal tissue is not going to weigh a 2 huge amount more than that a milliliter of water.</p> <p>3 Q. Okay.</p> <p>4 A. There will be a slight difference, but 5 it's not going to be a material difference.</p> <p>6 Q. Okay. Back to my page 1562, please.</p> <p>7 A. 1562.</p> <p>8 Q. Last page.</p> <p>9 There they're reporting that the topical 10 therapy seems predictably effective only if the 11 serum cyclosporin levels entered what is considered 12 to be therapeutic range of 50 to 300 nanograms per 13 ML.</p> <p>14 Do you see that?</p> <p>15 A. I do see that.</p> <p>16 Q. And if we look back to Kaswan, you see at 17 the top of page 653, it says that the intraocular 18 level speculated to be needed for control of uveitis 19 is 350 nanograms per ML. And it cites to the 20 Nussenblatt paper we've been looking at, right?</p> <p>21 A. I see that.</p> <p>22 Q. Isn't it true that Nussenblatt is talking 23 about serum levels, not levels in intraocular 24 levels?</p> <p>25 A. Nussenblatt talks about both. I see your</p> |

| | |
|---|---|
| <p style="text-align: right;">Page 142</p> <p>1 point, that the 50 to 300 refers to one of several</p> <p>2 conclusions of Nussenblatt, which is that when --</p> <p>3 that the topical cyclosporin did not produce high</p> <p>4 intraocular levels on its own due to poor --</p> <p>5 presumably poor transcorneal permeability. And,</p> <p>6 therefore, the anti-inflammatory effect of the</p> <p>7 topical cyclosporin drops in olive oil, I believe</p> <p>8 they used, was attributable to systemic absorption</p> <p>9 through the lacrimal system because rats are small.</p> <p>10 And so the effectiveness correlated with</p> <p>11 serum levels rather than, you know, strictly</p> <p>12 speaking, intraocular levels because they did not</p> <p>13 measure levels in the solid tissue of the eye.</p> <p>14 But the other arm of the study -- another</p> <p>15 arm of the study where they looked at these</p> <p>16 intravitreal injections did show a correlation</p> <p>17 between clinical effectiveness and intravitreal</p> <p>18 concentrations in the 160 to 580 nanograms per</p> <p>19 either ML or gram range. And that is looking at an</p> <p>20 intraocular tissue.</p> <p>21 So, you know, those are two of the data</p> <p>22 points from this study. So we can quibble over</p> <p>23 whether it's 50 to 300 or whether it's 160 to 580 or</p> <p>24 whether it's 100 to 400, but, you know, all of these</p> <p>25 are in comparable ranges and -- and that's my point.</p> | <p style="text-align: right;">Page 144</p> <p>1 disease or disease model; it was really a</p> <p>2 pharmacokinetic study.</p> <p>3 Q. And if you look at Kaswan at 653, it also</p> <p>4 said -- in the right-hand column, there's a</p> <p>5 paragraph that starts "Topical CsA"?</p> <p>6 A. Yes.</p> <p>7 Q. And it says: "In dogs with KCS, topical</p> <p>8 CsA ameliorated the chronic keratitis and increased</p> <p>9 the average Schirmer test by 9 millimeters per</p> <p>10 minute."</p> <p>11 Do you see that?</p> <p>12 A. I see that.</p> <p>13 Q. Is there any indication there of what</p> <p>14 levels increase Schirmer test scores?</p> <p>15 A. What levels of?</p> <p>16 Q. CsA.</p> <p>17 A. You mean topical -- you mean tissue</p> <p>18 levels?</p> <p>19 Q. Yes.</p> <p>20 A. I haven't pulled that particular paper,</p> <p>21 No. 17, I don't believe. It's another Kaswan paper</p> <p>22 from 1987.</p> <p>23 I don't know how to answer the question</p> <p>24 other than I don't see anything in that paragraph</p> <p>25 about specific tissue levels.</p> |
| <p style="text-align: right;">Page 143</p> <p>1 Q. But the ranges reported, for instance, in</p> <p>2 Nussenblatt, 50 to 300, are in serum, not in the</p> <p>3 solid tissue?</p> <p>4 A. Well, I think I really just answered that</p> <p>5 in my last paragraph. So, again, the range in</p> <p>6 ocular tissue in a similar assay in the same paper</p> <p>7 was 160 to 580 --</p> <p>8 Q. Is that a solid tissue or --</p> <p>9 MR. MILLS: Let's try not to talk over</p> <p>10 each other and interrupt. I don't think that</p> <p>11 Dr. Calman was finished with his answer.</p> <p>12 THE WITNESS: The vitreous is a semisolid</p> <p>13 tissue. As I've discussed, it's a gel. It has</p> <p>14 characteristics of both liquid and solid.</p> <p>15 BY MR. KANE:</p> <p>16 Q. Okay. And all of these papers that we've</p> <p>17 just looked at, I believe -- excuse me --</p> <p>18 Nussenblatt and Kaswan relate to uveitis?</p> <p>19 A. Nussenblatt relates to experimental</p> <p>20 autoimmune uveitis.</p> <p>21 And Kaswan, I don't know that it</p> <p>22 specifically -- let's see. They speculate that it</p> <p>23 might be possible to treat intraocular diseases such</p> <p>24 as immune mediated uveitis with topical application.</p> <p>25 But this particular study was not looking at a</p> | <p style="text-align: right;">Page 145</p> <p>1 Q. Okay.</p> <p>2 A. This paper is about tissue levels,</p> <p>3 obviously.</p> <p>4 Q. And does Nussenblatt say anything about</p> <p>5 the required concentration of CsA in intraocular</p> <p>6 tissues needed to treat dry eye syndrome?</p> <p>7 A. It's sort of a nonsensical question</p> <p>8 because dry eye is an ocular surface condition, not</p> <p>9 an intraocular condition.</p> <p>10 Q. Okay. Does Kaswan say anything about the</p> <p>11 required CsA concentration in ocular tissues for</p> <p>12 treatment of dry eye syndrome?</p> <p>13 A. Well, it does certainly talk about the</p> <p>14 very high levels of cyclosporin achieved in certain</p> <p>15 tissues that are relevant for dry eye, including a</p> <p>16 lacrimal gland and cornea. But it -- and it does</p> <p>17 mention in the first paragraph of the paper that --</p> <p>18 it does talk about recently systemically</p> <p>19 administered CsA has been found to be beneficial in</p> <p>20 Sjogren's syndrome, S-J-O-G-R-E-N-'S, which is a</p> <p>21 subset of aqueous-deficient dry eye. And so it does</p> <p>22 talk about that explicitly.</p> <p>23 It also in the very next sentence mentions</p> <p>24 keratoconjunctivitis sicca, which is KCS.</p> <p>25 And then in the very next paragraph, it</p> |

| | |
|--|--|
| <p style="text-align: right;">Page 146</p> <p>1 talks about the efficacy of topically applied CsA 2 for external ocular disorders. 3 So I think this paper is actually very 4 much responsive to an inquiry as to tissue levels of 5 cyclosporin in relevant tissues in rabbits, which 6 are typical species that's used for these 7 investigations, with a -- with a view towards 8 ameliorating Sjogren's syndrome and KCS, among other 9 things. 10 Q. I had a question. My question was about 11 Kaswan, but that's -- 12 A. Well, I'm on Kaswan. 13 Q. No, you're looking at Nussenblatt. 14 A. No, I'm looking at Kaswan. 15 Q. Oh, sorry. 16 A. I can start up -- 17 Q. No, that's fine. I misrepresented. Okay. 18 My question, though, was whether Kaswan 19 says anything about the required concentration of 20 CsA in ocular tissue for treatment of dry eye 21 syndrome. 22 MR. MILLS: Objection. Form. 23 THE WITNESS: Yeah, you're trying to 24 combine a whole bunch of different things. This -- 25 this paper talks about, in its introduction, the</p> | <p style="text-align: right;">Page 148</p> <p>1 dry eye are extremely high. 2 BY MR. KANE: 3 Q. Does Nussenblatt say anything about the 4 required concentration of CsA in ocular tissues for 5 treatment of dry eye syndrome? 6 A. Nussenblatt was designed to look at 7 experimental autoimmune uveitis. So it's not -- it 8 wasn't designed to look at dry eye and it doesn't 9 talk about dry eye, although some of the conclusions 10 from it may be relevant. But it doesn't explicitly 11 discuss dry eye. 12 Q. And if we look at Oellerich, same 13 question. Does Oellerich provide any information 14 about the required level of CsA in ocular tissues 15 for treatment of dry eye? 16 A. Well, Oellerich states that the levels 17 required for effective treatment of rejection in a 18 wide variety of tissues are similar. And it 19 discloses ranges, which I've roughly summarized as 20 roughly 100 to 400 nanograms per ML or, as they 21 express it, micrograms per liter, which is the same 22 thing. They did not look specifically in the eyes 23 or at dry eyes. 24 But, again, this is not -- it's not a high 25 school student but a POSA, a person that would</p> |
| <p style="text-align: right;">Page 147</p> <p>1 applicability of cyclosporin to KCS and Sjogren's 2 syndrome. And it talks about tissue levels, and it 3 also talks about minimal therapeutic levels of -- 4 they quote 50 to 300 quoting -- citing Nussenblatt. 5 So I -- you know, I think parts of the 6 paper are quite relevant, particularly the average 7 level of cyclosporin of 2850 -- 2,850 nanograms per 8 gram, and the very high levels in the cornea, well 9 over a thousand nanograms per gram for the first few 10 days after administration. 11 So, you know, it doesn't -- it wasn't 12 designed to specifically answer your question 13 because it's not in a disease model of KCS, but it 14 is looking at tissue levels and tissues of interest. 15 And it's explicitly designed for the purpose of 16 understanding how topical CsA would be useful in KCS 17 as well as other disorders. 18 BY MR. KANE: 19 Q. But it doesn't answer the question that I 20 asked, right? 21 MR. MILLS: Objection. Form. 22 THE WITNESS: So it is not a study of a 23 dry eye disease state. It is a pharmacokinetic 24 study that tells you what kind of levels you get. 25 And the levels you get in the tissues relevant to</p> | <p style="text-align: right;">Page 149</p> <p>1 understand that if a wide variety of tissues are 2 achieving adequate levels to control disease with 3 these types of levels in the blood, that these are 4 likely to be applicable to other types of tissue as 5 well. There was not a wide range of difference 6 between these different -- you know, different 7 levels. 8 So unless you posit there is some -- 9 something unique about a particular tissue that 10 would render these levels irrelevant, I think they 11 can be generalized to some degree. 12 Q. Is it your testimony that you can take 13 serum levels and apply those to solid tissue levels? 14 A. Well, I think that you can't directly 15 apply them. But I think that what you can say is, 16 for a variety of different tissues that were looked 17 at, there was no indication that there was a big 18 difference in the required levels for different 19 solid tissue. And what that suggests is that the 20 levels are not either being -- either dramatically 21 higher nor dramatically lower in the tissues than 22 they are in the bloodstream that supplies them. 23 Q. How do you reach that conclusion? 24 A. Well, for example, let's say that the 25 liver had an active transport mechanism that tended</p> |

| | |
|---|---|
| <p style="text-align: right;">Page 150</p> <p>1 to concentrate cyclosporin in tissue. You would 2 expect to be able to prevent liver transplant 3 rejection with a very high -- I mean, with a very 4 low level of serum cyclosporin because the liver was 5 actively concentrating it in the tissue. 6 I'm just saying hypothetically; I'm not 7 saying this is the case. 8 Let's say the kidney has an active 9 transport mechanism that pumps cyclosporin out of 10 the cells. Then you would expect that you would 11 need higher serum concentrations of cyclosporin to 12 see the same effect as far as preventing rejection. 13 Well, that's just not what they found. 14 And this is a very large data set from all over the 15 world. And the remarkable thing about this data 16 set, in my opinion, is its consistency both from 17 center to center and from tissue to tissue. 18 So, you know, that, to me, indicates that 19 it's not something particular to any particular type 20 of tissue. Nor have I read anything to suggest that 21 that is -- that there is such a concentration -- 22 concentrating or active transport mechanism in 23 either direction in any particular tissue type. 24 Furthermore, you know, the Nussenblatt 25 study indicates that the same range of serum</p> | <p style="text-align: right;">Page 152</p> <p>1 last column, you've got kidney, liver, heart, LU. 2 Let's look at the key here. 3 So there's a variety of different tissues 4 here: Kidney, heart, liver, lung, pancreas. And 5 then pediatric kidney, you know, pediatric liver. 6 So -- so that -- I just don't want to have 7 repeat the whole sentence. It's in the transcript. 8 I've explained how similar serum levels are required 9 for efficacy in a variety of solid tissues, which 10 indicates that -- including the eye as based on 11 Nussenblatt, which indicates there is not something 12 magical about the eye or any other tissue that tends 13 to concentrate or reduce the concentration of 14 cyclosporin in tissue with regard -- compared to the 15 blood. 16 And, furthermore, in the Nussenblatt 17 study, we actually do have a comparison. You know, 18 we do have an actual tissue level of cyclosporin in 19 the vitreous which is very comparable. Instead of, 20 you know, 100 to 400, it's 160 to 580. You know, 21 we're in that same ballpark. 22 You know, I'm convinced as a scientist 23 reading the totality of this data that those are the 24 kinds of tissue levels that are adequate for 25 efficacy in a variety of tissues.</p> |
| <p style="text-align: right;">Page 151</p> <p>1 cyclosporin is -- for an intraocular condition is 2 similar to that for these other solid tissues. 3 Suggesting that the eye doesn't behave any 4 differently than any other organ. 5 Q. Well, Dr. Calman, I mean, what other solid 6 tissue are you referring to? In Oellerich, they're 7 talking about serum levels, right? 8 A. Well, they're talking about -- they're not 9 just talking about -- they're talking about serum 10 levels but -- again, I don't want to have to go 11 through my whole same explanation. But they're 12 looking at kidney liver, heart. Let me see what 13 else. 14 I think I've explained it. I'm sorry if 15 it wasn't clear. But I went through a whole long 16 explanation of the relationship between tissue 17 levels and serum levels. And so... 18 Q. But my question is -- let me just try to 19 ask it. 20 So all the levels that we've looked at, 21 for instance, in Table 2 of Oellerich, are serum 22 levels, right? 23 A. Yes. But they're serum levels with 24 relationship to preventing transplantation in 25 different types of disease. So if you look at the</p> | <p style="text-align: right;">Page 153</p> <p>1 MR. MILLS: Is it okay if we take a break? 2 MR. KANE: Sure. 3 (Off the record at 2:00 p.m. and back on 4 the record at 2:18 p.m.) 5 BY MR. KANE: 6 Q. Okay. So looking at your last answer 7 there, you say: "I'm convinced as a scientist 8 reading the totality of this data that those kinds 9 of issue levels are adequate for efficacy in a 10 variety of issues." 11 Do you agree with me that Oellerich 12 doesn't provide an indication of the -- let me start 13 over. 14 Oellerich doesn't say anything about -- 15 A. Oellerich. 16 Q. Oellerich does not say anything about 17 increasing tear production in dry eye patients? 18 A. Not explicitly, no. 19 Q. Okay. Do you agree with me that 20 Nussenblatt doesn't say anything about increasing 21 tear production in dry eye patients? 22 A. Not explicitly per se, no. 23 Q. And you would agree with me Kaswan does 24 not say anything about increasing tear production in 25 dry eye patients?</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 154</p> <p>1 A. Not explicitly per se, no.</p> <p>2 Q. And you would agree with me that Oellerich</p> <p>3 does not identify the concentration of CSI in ocular</p> <p>4 tissue necessary to increase tear production in</p> <p>5 dry eye patients?</p> <p>6 A. Well, again, I think I've mentioned --</p> <p>7 made it clear how I'm using the information from</p> <p>8 these various references to establish some</p> <p>9 conclusions. But there -- you know, not in the</p> <p>10 black and white of the four corners of this document</p> <p>11 it doesn't explicitly address that, no.</p> <p>12 Q. Okay. And you'd agree with me that</p> <p>13 Nussenblatt doesn't identify the concentration of</p> <p>14 CsA -- the concentration of CsA necessary in the</p> <p>15 ocular tissues to increase tear production in</p> <p>16 dry eye patients?</p> <p>17 A. Only by implication, not in black and</p> <p>18 white of the four corners of the document.</p> <p>19 Q. And you agree with me Kaswan does not</p> <p>20 identify the concentration of CsA necessary in</p> <p>21 ocular tissues to increase tear production in</p> <p>22 dry eye patients?</p> <p>23 A. Only by implication, not in black and</p> <p>24 white in the four corners of this document.</p> <p>25 Q. Okay. Okay.</p> | <p style="text-align: right;">Page 156</p> <p>1 important aspects of drug formulation, including</p> <p>2 topical drug formulations for ophthalmic disease.</p> <p>3 And I routinely review information about various</p> <p>4 topical ophthalmic products, including their</p> <p>5 formulation and excipients.</p> <p>6 And so I do have a level of expertise in</p> <p>7 the area, although it is true that I do not hold</p> <p>8 myself out as an expert in formulation per se.</p> <p>9 Q. Okay.</p> <p>10 A. And we discussed earlier today some of the</p> <p>11 various clinical research studies I was involved in</p> <p>12 where excipients and formulation were key aspects of</p> <p>13 the study design.</p> <p>14 Q. Okay. Do you recall in Dr. Loftsson's</p> <p>15 declaration, he offered opinions with respect to</p> <p>16 what a person of ordinary skill would expect the</p> <p>17 impact of increasing the amount of castor oil in the</p> <p>18 emulsion to have on bioavailability based upon</p> <p>19 thermodynamic principles?</p> <p>20 MR. MILLS: Objection. Form.</p> <p>21 THE WITNESS: If we're going to talk about</p> <p>22 the Loftsson declaration, I'd like to see it,</p> <p>23 please.</p> <p>24 BY MR. KANE:</p> <p>25 Q. Why don't we look at paragraph 76 of your</p> |
| <p style="text-align: right;">Page 155</p> <p>1 A. I think the other thing I would say about</p> <p>2 Kaswan is that there is -- excuse me -- about</p> <p>3 Nussenblatt is that it does provide at least some</p> <p>4 indirect evidence that the therapeutic range in</p> <p>5 local tissue as shown in Table 2 shows good</p> <p>6 correlation with the level -- the levels needed in</p> <p>7 serum to achieve or systemically to achieve</p> <p>8 therapeutic effect for the same disease. Which</p> <p>9 again suggests that there's not a major difference</p> <p>10 in tissue levels of cyclosporin compared to serum</p> <p>11 circulating levels.</p> <p>12 Q. Just one second. Sorry.</p> <p>13 Dr. Calman, you said earlier that you</p> <p>14 don't consider yourself an expert in ophthalmic</p> <p>15 formulations, correct?</p> <p>16 MR. MILLS: Objection. Form.</p> <p>17 THE WITNESS: That's not what I said. I</p> <p>18 said what I said. Say it again if you'd like.</p> <p>19 BY MR. KANE:</p> <p>20 Q. Okay. Go ahead.</p> <p>21 A. Well, I -- words to the effect that, you</p> <p>22 know, in my 12 years in research and basic research</p> <p>23 and 27 years in clinical ophthalmology, my</p> <p>24 knowledge, skills, experience, training, and</p> <p>25 education have given me an understanding of</p> | <p style="text-align: right;">Page 157</p> <p>1 declaration.</p> <p>2 Are you there?</p> <p>3 A. Yes.</p> <p>4 Q. Do you see there in the first sentence</p> <p>5 Dr. Loftsson asserts that the results of Allergan's</p> <p>6 confidential internal pharmacokinetic --</p> <p>7 A. I'm sorry. Which paragraph are we in?</p> <p>8 Q. 76.</p> <p>9 Why don't you just read that paragraph to</p> <p>10 yourself.</p> <p>11 A. Yeah.</p> <p>12 Q. Okay. And my question is simply: Are you</p> <p>13 offering any opinions as to what a person of</p> <p>14 ordinary skill would expect based on thermodynamic</p> <p>15 principles as described by Dr. Loftsson?</p> <p>16 MR. MILLS: Objection. Form.</p> <p>17 THE WITNESS: I have a general idea of the</p> <p>18 issues, and I am certainly deferring to Dr. Amiji as</p> <p>19 being far more expert in that field. And I know</p> <p>20 Dr. Loftsson is also very qualified in the area of</p> <p>21 thermodynamics. But I believe I am qualified to</p> <p>22 discuss these issues and as well to put them in</p> <p>23 clinical context which neither of them is a</p> <p>24 clinician.</p> <p>25</p> |

| | |
|--|---|
| <p style="text-align: right;">Page 158</p> <p>1 BY MR. KANE:</p> <p>2 Q. But are you deferring to Dr. Amiji with</p> <p>3 respect to the thermodynamic principles associated</p> <p>4 with the interaction between the CsA and the oil and</p> <p>5 the water emulsion?</p> <p>6 A. Let me just see what I did say in my</p> <p>7 report.</p> <p>8 You know, my -- there are aspects of this</p> <p>9 that all the experts are in agreement on. And then</p> <p>10 there are other aspects where I can provide a</p> <p>11 clinical context that's missing.</p> <p>12 And so with regard to any details or any</p> <p>13 equations regarding thermodynamic activity, I would</p> <p>14 defer to the formulators, doctors. But with regard</p> <p>15 to the relationship of the bioavailability to the</p> <p>16 clinical efficacy, I'm a clinician and they're not.</p> <p>17 Q. Okay.</p> <p>18 A. And so that was the focus of my -- of</p> <p>19 my -- my declaration with regard to this issue as</p> <p>20 well as the issues regarding comparison of disparate</p> <p>21 studies, which we discussed and I think Dr. Amiji</p> <p>22 also discussed. And Dr. Bloch as well.</p> <p>23 Q. Okay. So just a couple of follow-ups,</p> <p>24 then.</p> <p>25 Did you talk to counsel today on any of</p> | <p style="text-align: right;">Page 160</p> <p>1 in -- with relation to transplantations.</p> <p>2 Do you recall that?</p> <p>3 A. I do.</p> <p>4 Q. And I believe at some point you talked</p> <p>5 about that they were measuring concentrations for</p> <p>6 preventing transplantation in different tissue?</p> <p>7 A. Preventing rejection.</p> <p>8 Q. Preventing rejection of transplantation.</p> <p>9 Okay. And you were also asked questions</p> <p>10 regarding whether the Nussenblatt and Kaswan</p> <p>11 references explicitly disclose CsA concentrations</p> <p>12 that were therapeutically effective for</p> <p>13 tear production.</p> <p>14 Do you recall those questions?</p> <p>15 A. I do.</p> <p>16 Q. And I believe that you used the word "by</p> <p>17 implication"?</p> <p>18 A. Yes.</p> <p>19 Q. Can you tell us what you mean when you say</p> <p>20 "by implication"?</p> <p>21 A. I lot of this, I think, I went through in</p> <p>22 my declaration.</p> <p>23 Basically, the Nussenblatt paper and the</p> <p>24 Kaswan paper that references it are discussing what</p> <p>25 is believed in the field to be adequate</p> |
| <p style="text-align: right;">Page 159</p> <p>1 the breaks regarding the substance of your testimony</p> <p>2 today?</p> <p>3 A. No.</p> <p>4 Q. Okay. And you've brought some documents</p> <p>5 in we talked about earlier this morning.</p> <p>6 Did you have any other notes or</p> <p>7 handwritten annotations on those documents?</p> <p>8 A. Not on these documents, no.</p> <p>9 Q. On the documents that you brought?</p> <p>10 A. No.</p> <p>11 Q. They're just clean copies?</p> <p>12 A. Yes.</p> <p>13 MR. KANE: No further questions at this</p> <p>14 time.</p> <p>15 MR. MILLS: Let's take a short break.</p> <p>16 MR. KANE: Okay.</p> <p>17 (Off the record at 2:29 p.m. and back on</p> <p>18 the record at 2:36 p.m.)</p> <p>19 --o0o--</p> <p>20 EXAMINATION</p> <p>21 BY MR. MILLS:</p> <p>22 Q. Dr. Calman, I have just a couple of</p> <p>23 questions for you.</p> <p>24 Early in your testimony you were asked</p> <p>25 some questions about cyclosporin A concentrations</p> | <p style="text-align: right;">Page 161</p> <p>1 concentrations for uveitis, for example, which is an</p> <p>2 example of a severe ocular inflammatory condition.</p> <p>3 And, again, the -- the vitreous concentrations that</p> <p>4 were correlated with clinical efficacy in that</p> <p>5 Nussenblatt study were comparable to the serum</p> <p>6 levels of cyclosporin that correlated the efficacy</p> <p>7 both in that same EUA model and in a variety of</p> <p>8 different tissues with respect to transplant</p> <p>9 rejection.</p> <p>10 So I'm -- by implication, I'm using my</p> <p>11 knowledge and skill as a scientist to interpret the</p> <p>12 data in light of the other available information I</p> <p>13 would have as a POSA.</p> <p>14 Q. Just a moment ago you referred to uveitis</p> <p>15 as "a severe ocular inflammation"?</p> <p>16 A. I did. It's often a vision-threatening</p> <p>17 inflammation.</p> <p>18 Q. Earlier I think you used the phrase</p> <p>19 "high-powered inflammatory disease" with respect</p> <p>20 to --</p> <p>21 A. Let me give you an example.</p> <p>22 When we treat -- there are different types</p> <p>23 of ocular disease that we treat, for example, with</p> <p>24 steroids, steroid drops typically. Some of them</p> <p>25 require very high doses or high-frequency</p> |

| | |
|---|---|
| <p style="text-align: right;">Page 162</p> <p>1 administration. Others require very low doses or 2 low-frequency administration. 3 So examples of clinical entities where you 4 might use a very high concentration would be an 5 autoimmune keratitis or a uveitis where oftentimes 6 we're having patients put in our most potent steroid 7 every one to two hours, sometimes around the clock. 8 In contrast, there are other conditions 9 where we may use steroids, either short-term or 10 long-term, where much lower concentration or 11 frequency is effective. Examples of that include 12 KCS and certain types of ocular allergy where very 13 low dose, such as a once or twice a day of 14 administration of our lowest potency steroid drop, 15 may be sufficient for clinical effect. 16 So that was my -- that was my -- just 17 trying -- again, my job here in part is to put all 18 of these things into clinical context. 19 Q. Earlier you were asked a series of 20 questions by counsel regarding various efficacy 21 measures reported in the Sall reference. 22 Do you recall that? 23 A. I do. 24 Q. You were asked a series of questions about 25 which efficacy measures directly measure an increase</p> | <p style="text-align: right;">Page 164</p> <p>1 And Dr. Bloch did his own statistical 2 analysis to verify that there was no statistically 3 significant difference between the .05 and 4 .1 percent cyclosporin at any time point. 5 With regard to materiality of differences, 6 I'm unable to assess that for the Schirmer's without 7 anesthesia because no numbers were provided. So I 8 don't know. 9 I'm just -- to put that -- again, put that 10 in clinical context, you can have a statistically 11 significant increase in some variable without having 12 it be material. And an example of that is where we 13 do have some numbers in the Schirmer's with 14 anesthesia, not to recapitulate that entire 15 discussion, but these changes were small. These 16 changes were the most -- at the most, 0.4 for 17 Schirmer, quote/unquote, units corresponding to a 18 small increase in actual Schirmer score on the order 19 of 2 millimeters. Maybe it's 1, maybe it's 3, maybe 20 it's 2. None of those are, in my experience, 21 material. 22 Q. Earlier in your testimony I believe you 23 used the word "pivotal" at some point in referencing 24 the Phase 3 studies reported in Sall; is that 25 correct?</p> |
| <p style="text-align: right;">Page 163</p> <p>1 in tear production. 2 Do you recall those questions? 3 A. Yes. 4 Q. My question is whether any of the efficacy 5 measures in Sall -- as they were reported in Sall 6 demonstrate a significant or material increase in 7 tear production in the 0.05 percent CsA formulation 8 as compared to the 0.1 percent CsA formulation. 9 A. Well, what Sall tells us is, with respect 10 to the overall tear secretion capacity of the eye as 11 measured by Schirmer's without anesthesia, that 12 there were no significant differences between the 13 groups and that all of the groups, including 14 vehicle, had a statistically significant increase 15 over baseline at each time point, which included 16 Months 1, 3, 4, and 6. 17 With regard to Schirmer's with anesthesia, 18 this was only performed at Months 3 and 6. 19 And, by the way, what I've just talked 20 about, those were categorized. 21 And with regard to Schirmer's with 22 anesthesia, which was also categorized, the raw 23 value not reported in Sall, there was no 24 statistically significant difference reported 25 between the .05 and the .1.</p> | <p style="text-align: right;">Page 165</p> <p>1 A. Yes. 2 Q. When you use the word "pivotal," what do 3 you mean by that? 4 A. Typically the FDA requires two large 5 well-controlled clinical trials in humans before 6 they will approve a new drug as safe and effective. 7 Now, there may be -- and there's a lot more to it 8 than that in terms of what the controls need to be 9 and so forth, but that's the big picture. There may 10 be exceptions, particularly for rare diseases, but 11 that's the general way that drugs get approved by 12 the FDA. 13 Q. When you used the word "pivotal," were you 14 comparing the Phase 3 trials for Restasis to some 15 other Phase 3 trials and saying that the Restasis 16 trials were more impressive or something of that 17 nature? 18 A. Well, again now, "pivotal" is a term of 19 art, and I have not researched the term. But as I 20 understand it, pivotal trials are those Phase 3 21 trials typically sponsored by a drug manufacturer 22 and submitted to the FDA in support of approval of 23 the drug. 24 Q. Do you recall earlier being asked 25 questions regarding the claim construction that you</p> |

| | |
|---|--|
| <p style="text-align: right;">Page 166</p> <p>1 understood to apply in the IPR proceedings?</p> <p>2 A. Yes.</p> <p>3 Q. And do you recall being asked questions</p> <p>4 regarding that that claim construction involved that</p> <p>5 therapeutic efficacy could include palliative</p> <p>6 treatments?</p> <p>7 A. Yes.</p> <p>8 Q. If that claim construction in a</p> <p>9 hypothetical excluded palliative treatments, would</p> <p>10 that change your opinions in this case? If you</p> <p>11 know.</p> <p>12 A. I think it would depend on your definition</p> <p>13 of "palliative," and I think there's been a lot of</p> <p>14 confusion about these terms: Palliative,</p> <p>15 therapeutic, and curative.</p> <p>16 The one thing that I can say I think that</p> <p>17 we probably would all agree on is that a treatment</p> <p>18 is only curative if the disease is still cured after</p> <p>19 you withdraw it.</p> <p>20 So I'm not sure I -- I don't have this...</p> <p>21 And I think the other thing I've talked</p> <p>22 about previously is that there are steps in the</p> <p>23 pathophysiologic change. So if you think about a</p> <p>24 patient who has rheumatoid arthritis, Sjogren's</p> <p>25 syndrome, and KCS and complains of dry eye, a</p> | <p style="text-align: right;">Page 168</p> <p>1 --o0o--</p> <p>2 EXAMINATION</p> <p>3 BY MR. KANE:</p> <p>4 Q. Dr. Calman, did you discuss with counsel</p> <p>5 the questions he was going to ask you during the</p> <p>6 break?</p> <p>7 A. No.</p> <p>8 Q. And one question which I should have asked</p> <p>9 earlier but I didn't. In your list of exhibits, you</p> <p>10 list the deposition transcript of Dr. Sheppard. I</p> <p>11 think you cite that in your report Exhibit 57,</p> <p>12 page 58.</p> <p>13 A. I see that.</p> <p>14 Q. Okay. And my question is simply: Did you</p> <p>15 read any of the transcripts from Dr. Loftsson,</p> <p>16 Dr. Schiffman, or Dr. Attar prior to preparing your</p> <p>17 opinions?</p> <p>18 A. Well, in preparation for the IPR, I read</p> <p>19 the transcript of Dr. Loftsson. I read the</p> <p>20 declarations of Dr. Schiffman and Dr. Attar. I did</p> <p>21 not read any transcripts, deposition transcripts,</p> <p>22 for Dr. Schiffman or Attar for the purpose of the</p> <p>23 IPR.</p> <p>24 MR. KANE: Okay. No further questions.</p> <p>25 MR. MILLS: This will be very brief.</p> |
| <p style="text-align: right;">Page 167</p> <p>1 curative treatment would cure his, or her,</p> <p>2 rheumatoid arthritis which, unfortunately, we don't</p> <p>3 have.</p> <p>4 You can treat the rheumatoid arthritis or</p> <p>5 you can treat the Sjogren's syndrome which is</p> <p>6 downstream. Or you can treat the KCS which is</p> <p>7 downstream from that. Or you can treat the ocular</p> <p>8 surface drying which is downstream from that, such</p> <p>9 as with artificial tears.</p> <p>10 So what's palliative and what's</p> <p>11 therapeutic, I don't see it as quite as much of a</p> <p>12 bright line as some of the opposing experts do.</p> <p>13 Q. As you understand the term "curative," is</p> <p>14 Restasis a curative treatment?</p> <p>15 A. Well, no, because if you stop the</p> <p>16 treatment, the problems comes back and you have to</p> <p>17 restart.</p> <p>18 Q. Dr. Calman, who was responsible for the</p> <p>19 opinions expressed in your declaration?</p> <p>20 A. I am.</p> <p>21 Q. Anyone else?</p> <p>22 A. No.</p> <p>23 MR. MILLS: Thank you, Dr. Calman.</p> <p>24 MR. KANE: I just have a couple of quick</p> <p>25 follow-up questions.</p> | <p style="text-align: right;">Page 169</p> <p>1 Sorry.</p> <p>2 MR. KANE: Okay.</p> <p>3 --o0o--</p> <p>4 EXAMINATION</p> <p>5 BY MR. MILLS:</p> <p>6 Q. Dr. Calman, please take a look at</p> <p>7 paragraph 58 of your declaration.</p> <p>8 A. Okay.</p> <p>9 Q. And on page 38 --</p> <p>10 A. Okay.</p> <p>11 Q. -- the second to the last bullet from the</p> <p>12 bottom.</p> <p>13 A. Okay.</p> <p>14 Q. In that paragraph, do you cite the</p> <p>15 Schiffman deposition transcript?</p> <p>16 A. Okay. I do. So I guess I did read it.</p> <p>17 I'm sorry. I thought I read it for -- the</p> <p>18 reason I was careful how I answered your question</p> <p>19 was I know I've read his depositions, and I thought</p> <p>20 it was in preparation for the district court case.</p> <p>21 And, yeah, I did include a quote -- or not</p> <p>22 a quote, but I did -- this issue, we actually</p> <p>23 discussed this issue, the fact that Figure 4 it</p> <p>24 looks like Figure 3. We actually did discuss that</p> <p>25 earlier and that is the reference, yes. I apologize</p> |

Page 170

1 for that confusion on my part.

2 Q. Let me just ask you this: If you cited to

3 a particular transcript in your declaration, does

4 that indicate that you saw that transcript at some

5 point?

6 A. Yes.

7 MR. MILLS: Okay. Thank you.

8 MR. KANE: No questions.

9 THE REPORTER: I can have the final to you

10 Friday. And will send you a rough tonight.

11 MS. FRANCIS: Thanks.

12 MR. MILLS: Yes.

13 THE REPORTER: Thank you.

14 (Whereupon, the deposition was

15 adjourned at 2:49 p.m.)

16 --o0o--

Page 172

1 I, MEGAN F. ALVAREZ, a Certified Shorthand

2 Reporter, License No. 12470, certify:

3 That, prior to being examined, the witness

4 named in the foregoing proceeding, to wit, ANDREW F.

5 CALMAN, M.D., PH.D., was by me duly sworn to testify to

6 the truth, the whole truth, and nothing but the truth;

7 That said transcript was taken down in

8 shorthand by me, on Wednesday, July 12, 2017, at

9 9:08 A.M., before the following adverse parties:

10 MICHAEL J. KANE, ESQ., representing the Patent Owner;

11 and JAD A. MILLS, ESQ., for the Respondent; and GARY

12 SPEIER, ESQ., for all other Petitioners, and was

13 thereafter reduced to computerized transcription under

14 my direction and is a true record of the testimony;

15 I certify that I have not been disqualified as

16 specified under Rule 28 of the Federal Rules of Civil

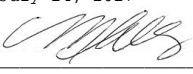
17 Procedure.

18 I further certify that I am not interested in

19 the event of the action.

20

21 DATED: July 14, 2017

22 

23 _____

24 MEGAN F. ALVAREZ

25 RPR, CSR 12470

Page 171

1

2 I declare under penalty of perjury that the

3 foregoing is true and correct. Subscribed at

4 _____, California, this _____ day of

5 _____, 2017.

6

7 _____

8

9

10 ANDREW F. CALMAN, M.D., PH.D.

1 Errata Sheet

2

3 NAME OF CASE: MYLAN PHARMACEUTICALS INC. v. ALLERGAN

4 DATE OF DEPOSITION: 07/12/2017

5 NAME OF WITNESS: ANDREW F. CALMAN, M.D., PH.D.

6 Reason Codes:

7 1. To clarify the record.

8 2. To conform to the facts.

9 3. To correct transcription errors.

10 Page _____ Line _____ Reason _____

11 From _____ to _____

12 Page _____ Line _____ Reason _____

13 From _____ to _____

14 Page _____ Line _____ Reason _____

15 From _____ to _____

16 Page _____ Line _____ Reason _____

17 From _____ to _____

18 Page _____ Line _____ Reason _____

19 From _____ to _____

20 Page _____ Line _____ Reason _____

21 From _____ to _____

22 Page _____ Line _____ Reason _____

23 From _____ to _____

24

25 _____

| | | | |
|--|--|--|--|
| <hr/> <p>-</p> <hr/> <p>--o0o--</p> <p>112:1 113:2 159:19 168:1 169:3 170:16</p> <hr/> <p>0</p> <hr/> <p>0.008 55:13</p> <p>0.009 61:11</p> <p>0.014 59:19 61:8</p> <p>0.044 55:11</p> <p>0.05 55:12,24 56:22 57:10 61:10 63:9 72:11 77:23 92:15 109:7 115:11,15, 22 116:15,24 163:7</p> <p>0.062 55:15</p> <p>0.09 92:15</p> <p>0.1 50:20 51:5 55:17,25 56:23 65:13 72:13 92:18 109:10 115:11,16,23 116:16,25 163:8</p> <p>0.10 92:17</p> <p>0.25 105:10,15</p> <p>0.39 108:14</p> <p>0.4 164:16</p> <p>0.40 105:9</p> <p>0.5 50:19 51:2 54:22 56:1 57:11 65:12 115:10</p> <p>0025 122:4</p> | <p>009 63:10,24,25</p> <p>01 72:23</p> <p>014 63:21</p> <p>025 106:1</p> <p>05 54:25 55:1,24 56:1,5,8, 18 57:7,15 58:3,4 62:2 63:20,22,25 65:21 72:24 84:20 110:10,20,25 116:3,7 117:21 121:7,9, 14,22,23 122:5 163:25 164:3</p> <p>09 95:10 108:9</p> <hr/> <p>1</p> <hr/> <p>1 27:12 53:6 55:18 56:10, 16,18 57:1,6 58:4,19 60:12 72:23 74:15 81:4 84:19 85:14 96:18 98:1 105:3,11,16 106:14,18 110:10,19 111:6,8,11,19 116:4 117:21 121:10 135:24 136:1 138:17 163:16,25 164:4,19</p> <p>1-millimeter 110:19</p> <p>1.6 105:7,11 111:6,12</p> <p>1.6-millimeter 110:20</p> <p>1.94 107:25</p> <p>1/2 111:19</p> <p>1/20th 122:4</p> <p>10 39:22 40:5 66:20 87:7 92:6 95:11 96:20 97:2,9 101:5 111:20 113:9,20, 25 118:6 123:24</p> | <p>10-millimeter 66:16 87:24 110:25 118:11 119:12 120:1,11</p> <p>100 62:10 63:4 137:5 142:24 148:20 152:20</p> <p>1001 33:3</p> <p>1002 33:6 71:14</p> <p>1004 33:11</p> <p>1006 34:2</p> <p>1007 49:24</p> <p>1011 127:12 131:14,15 133:4</p> <p>1039 13:24 39:23,25 80:20</p> <p>103:1559 133:16</p> <p>1040 72:1</p> <p>1042 21:25</p> <p>1058 125:12</p> <p>10:10 44:9</p> <p>11 26:2 41:5 42:1</p> <p>11:07 80:16</p> <p>11:21 80:17</p> <p>12 7:1 22:18 23:12 26:4 113:1 155:22</p> <p>12:02 108:24</p> <p>12:05 111:25</p> <p>12:49 113:1</p> | <p>15 31:15 59:12 67:6 110:24 118:13,16 119:12 120:20,21 124:1 127:24</p> <p>1561 135:20</p> <p>1562 134:20 141:6,7</p> <p>16 9:20</p> <p>160 136:13,20 137:5 142:18, 23 143:7 152:20</p> <p>17 144:21</p> <p>18 7:20 8:23</p> <p>1985 134:6</p> <p>1987 144:22</p> <p>1994 103:24</p> <p>1995 133:17</p> <p>1999 87:19</p> <hr/> <p>2</p> <hr/> <p>2 24:11 27:12 57:10 59:23 60:11 64:2 65:1,12 72:7, 17 89:14 92:12 93:23 96:18,24,25 97:22,23 98:1,7,14 100:18 102:24 106:19 108:8 109:22 111:19 126:5 135:20 136:9 137:15 138:13 139:7 151:21 155:5 164:19,20</p> <p>2,850 147:7</p> <p>2- 101:7</p> <p>2.11 107:25</p> |
|--|--|--|--|

| | | | |
|---|---|--|---|
| 2.9 60:13 | 27:11 50:8 58:1,8,19 59:17,18,25 60:10 61:7 67:25 72:25 76:2 77:14, 17,20,22 78:4 80:5,24 90:18 92:13 96:18 97:1, 6,24 98:7 99:4 100:19, 21,24 101:2,5 103:16,19 106:21 108:9 118:12 163:16,18 164:19,24 165:14,15,20 169:24 | 103:18 | 632 50:12 |
| 20 14:22 31:15 59:12 62:13, 14,16 121:10,16,18,19 122:1 | | 4.5 99:6 | 635 53:7 55:19 108:6 |
| 200 62:10 128:22 | | 400 137:5 142:24 148:20 152:20 | 637 73:18 |
| 2002 49:16,18,21 87:21 | 3-millimeter 60:14 101:8 111:15 | 42 16:15 | 651 126:5 |
| 2003 87:22 127:24 | | <hr/> 5 <hr/> | 652 128:2,5,12 |
| 2008 49:6 86:23 88:21 113:8, 13,14 118:3 | 3.25 97:7 | 5 66:17 67:8 78:4 87:3,5 88:21 89:2 90:20 98:8 99:6 106:20 114:6 124:2 | 653 128:2,5,9,19 141:17 144:3 |
| 2017 7:1 14:9 16:20 113:1 | 3.5 97:8 99:5 | 5.5 99:6 | 67 89:8,11 92:9 95:9 |
| 2077 132:24 133:1,6 134:2 | 3.75 97:8 | 50 62:10 96:9 128:14,25 130:1 135:5,12,17 137:4 141:12 142:1,23 143:2 147:4 | 68 89:17 96:24 100:12 105:1 |
| 2480 7:14 | 30 14:22 136:17,23 | 500 138:2,5,7 | 69 107:22 129:5 |
| 25 105:2,22 106:13 | 300 128:14,25 135:5,12,17 137:4 141:12 142:1,23 143:2 147:4 | 500-milligram 136:3 | <hr/> 7 <hr/> |
| 27 22:17,18 155:23 | 30th 14:9 | 55 14:6 18:25 | 7 97:1,6 100:14,22 111:20 117:20 |
| 27-plus 20:24 | 32 70:9 | 56 31:19 | 71 89:11 |
| 2850 147:7 | 33 70:9 110:3 | 57 168:11 | 73 113:4,18 115:2,6 |
| 29 16:20 70:4 | 34 47:10 70:12 | 58 80:11,20 88:18 168:12 169:7 | 74 116:13 |
| 2:00 153:3 | 350 130:2 141:19 | 580 136:13,20 137:5 139:2 142:18,23 143:7 152:20 | 76 156:25 157:8 |
| 2:18 153:4 | 37 46:13 | <hr/> 6 <hr/> | 77 72:2 108:20,21 110:3 |
| 2:29 159:17 | 38 169:9 | 6 55:5,13,17,23 57:8 58:20 108:14 110:20 132:16 133:12,20 163:16,18 | 78 124:21 |
| 2:36 159:18 | <hr/> 4 <hr/> | <hr/> 6 <hr/> | 79 127:18 |
| 2:49 170:15 | 4 27:11 55:12 56:15 57:7 58:20 72:25 76:14 77:7,8 78:4 79:3 98:7 99:5 163:16 169:23 | 600 128:22 | <hr/> 8 <hr/> |
| <hr/> 3 <hr/> | 4-millimeter | | 8 21:24 97:7 100:14,25 106:20 117:20 |
| 3 | | | |

| | | | |
|--|---|--|---|
| 8/5ths 105:10 | access 75:2 | adequate 149:2 152:24 153:9 160:25 | 158:9 |
| 80 136:17,23 | accessory 42:24 | adheres 53:24 | agrees 81:21 |
| 80-microgram 136:1 | account 116:21 | adjourned 170:15 | ahead 155:20 |
| 800 136:10 138:3 | accuracy 95:22 | adjust 98:6 | Akorn 38:3 |
| <hr/> 9 <hr/> | accurate 12:10 16:22 94:7 95:3 | administered 137:11 145:19 | Alcon 26:14 |
| 9 97:8 101:3 144:9 | accustomed 60:3 | administration 147:10 162:1,2,14 | Allergan 9:5 10:13,15 57:23 59:7 80:23 89:25 94:17 97:20 99:9 110:8 |
| 930 33:12,16 | achieve 57:24,25 118:14 155:7 | admissible 71:6 | Allergan's 64:19 71:4 133:6 157:5 |
| 94110 7:15 | achieved 56:7 110:25 145:14 | admitted 103:22 111:9 | allergy 162:12 |
| 9:08 7:1 | achieving 149:2 | admitting 17:7 | alluding 48:24 |
| 9:57 44:8 | acquired 21:6 22:21,25 | advised 40:6 | Altman 15:11 |
| <hr/> A <hr/> | active 31:1 149:25 150:8,22 | aesthetic 104:17 | ameliorated 144:8 |
| A-m-i-j-i 32:13 | actively 150:5 | affect 78:12 96:13 98:9 | ameliorating 146:8 |
| A-r-c-h 133:13,14 | activity 158:13 | AFTERNOON 113:1 | Amiji 32:13 33:2,6 36:7,22 37:6 69:24 71:12,13 108:22 109:7 157:18 158:2,21 |
| A-r-c-h-o-p-h-t-h-a-l-m-o-l 133:16 | actual 40:16 72:24 75:7,13 94:18 98:24 101:21 102:17,18 152:18 164:18 | aggravate 31:4 | Amiji's 70:3 72:3,16 73:11 108:20 133:4 |
| a.m. 7:1 44:8,9 80:16,17 | acuity 77:12 | ago 19:3 23:4,8,12 24:11 30:21 31:16 33:15 36:15 72:21 90:9 161:14 | amount 45:15,16,22 46:3 53:20 117:11 141:2 156:17 |
| ability 20:1,9 64:10 | add 26:12 72:20 | agree 45:11 50:18 51:10 59:16 60:20 61:13,17 63:8 64:25 65:11 72:16 73:3 74:9 75:18 77:22 81:7 82:9,22 83:10,23 84:10, 25 85:22 86:11 98:12 113:23 116:10 123:8 125:16 153:11,19,23 154:2,12,19 166:17 | analyses 122:9 |
| able 30:16 35:5 96:7 150:2 | addition 72:20 75:5 108:10,15 | agreeing 73:15 | analysis 17:14 20:11 28:18 61:15 66:11 73:14 91:9 93:10 95:24 97:13 98:9 102:19 105:24 106:9,17,23,24 107:1,4 109:22 110:8,12 111:12 164:2 |
| abnormal 63:5,6 | additional 18:10 21:16 26:12 60:17 94:5 | agreement | analyze |
| absence 43:17 103:12 110:17 | address 7:12 70:10 154:11 | | |
| absorption 142:8 | addressed 69:24 | | |
| accept 95:6 | addresses 70:12 | | |

| | | | |
|---|--|---|---|
| <p>94:4 123:13</p> <p>analyzing 90:3</p> <p>anatomically 139:12</p> <p>and/or 34:14,18</p> <p>Andrew 7:3,11</p> <p>anesthesia 44:24 45:3,4,7,14,18,21 46:5,19,24 47:18,22 57:18 58:22,24 60:23 64:9,13,15 74:1,18,19 75:8 81:17,18 104:3,10 113:19,22,23 114:4,10, 24 163:11,17,22 164:7, 14</p> <p>anesthetic 104:5</p> <p>animal 139:17,24 141:1</p> <p>animals 28:19</p> <p>Anna 12:24 15:10</p> <p>annotations 159:7</p> <p>answer 7:25 8:12,20 20:8 40:15 69:11 70:10 75:5 82:12, 25 94:3,6,11 98:19 122:21 124:10 138:11 139:6 143:11 144:23 147:12,19 153:6</p> <p>answered 53:1 65:3 80:8 143:4 169:18</p> <p>answering 15:19 68:13</p> <p>answers 7:24</p> <p>anterior 131:7</p> <p>anti-inflammatory 67:10 131:10 137:2 142:6</p> | <p>antibiotic 10:11</p> <p>anticipate 132:10</p> <p>anticipated 132:14</p> <p>antitrust 9:16 10:7</p> <p>Anybody 13:4</p> <p>anyway 22:7</p> <p>apologetic 107:7</p> <p>apologize 169:25</p> <p>Apotex 10:13,16 37:25</p> <p>apparent 75:16</p> <p>apparently 62:11</p> <p>Appeals 11:25</p> <p>appear 75:25 121:22 134:2</p> <p>appears 61:17 76:13 80:4</p> <p>appendix 31:19 32:18 34:5</p> <p>applicability 147:1</p> <p>applicable 20:9 149:4</p> <p>applicants 38:5</p> <p>application 22:23 23:4,5,14 33:21 143:24</p> <p>applied 23:22 27:22 146:1</p> <p>apply 18:16 20:1 41:21,22 149:13,15 166:1</p> | <p>applying 41:17 61:22 63:16</p> <p>approached 56:8</p> <p>appropriate 39:16 62:4 106:7</p> <p>approval 87:9 88:5 165:22</p> <p>approve 165:6</p> <p>approved 48:2 49:14 87:19,21 122:23 165:11</p> <p>approving 66:1 68:2 123:8</p> <p>approximately 8:16 14:18 67:6,8 105:2, 9,15 106:15 124:1</p> <p>approximation 43:12 45:10 46:6 58:16 104:9 114:22</p> <p>aqueous 46:20,25 47:21 129:15, 17,18,20 130:2 131:8,23 132:2,4,6 137:22,23 138:18 139:4,8,10,13 140:18</p> <p>aqueous-deficient 29:9 145:21</p> <p>arbitrarily 98:5</p> <p>arbitrary 91:4 98:23</p> <p>Archives 132:21 133:15,22</p> <p>area 23:1 43:5 85:14 156:7 157:20</p> <p>areas 33:10 54:4,6 91:25</p> <p>aren't 77:7 126:20</p> <p>Argentum 38:22</p> <p>argumentative 48:20 99:16</p> | <p>arguments 116:21</p> <p>arm 142:14,15</p> <p>art 12:17 13:13 52:22 70:6 165:19</p> <p>arthritis 166:24 167:2,4</p> <p>article 75:4 127:16 133:12 134:2,4</p> <p>articles 18:7</p> <p>artificial 76:23,24 79:6,14 80:1 85:16 167:9</p> <p>asked 53:4 59:4 91:13 92:4 94:1 99:13,24 147:20 159:24 160:9 162:19,24 165:24 166:3 168:8</p> <p>asking 87:11 88:23 95:14,17 105:13 132:11 133:19, 20,21,22,24 140:8,9</p> <p>aspect 88:15</p> <p>aspects 114:16 156:1,12 158:8, 10</p> <p>assay 143:6</p> <p>asserting 57:5 119:11</p> <p>asserts 157:5</p> <p>assess 164:6</p> <p>assessment 84:22 85:4</p> <p>assigned 97:1,6,7,8,9 98:13</p> <p>associate 21:13</p> |
|---|--|---|---|

| | | | |
|--|--|---|--|
| associated 29:19 119:5 158:3 assume 23:13 33:4 assuming 52:19 Attar 70:17 127:22 168:16,20, 22 Attar's 124:23 attempt 32:20 61:3 89:13 91:1,3 102:2 103:7 121:6 attempted 65:6 103:2 110:17 attention 35:2 attributable 142:8 authors 61:2 75:18 autoimmune 136:25 143:20 148:7 162:5 available 36:5 66:2,13 67:15 68:12 69:5,13 88:11 107:1 161:12 average 65:18 72:11 79:5,14 92:12 99:1 105:25 106:12,14,15 109:8 110:18 111:4,16 121:21 144:9 147:6 avoided 94:17 aware 13:5 15:5,13 38:24 49:2, 4 68:21 102:16 <hr/> <p style="text-align: center;">B</p> <hr/> B-l-e-p-h-a-r-i-t-i-s 83:3 B-l-o-c-h 32:14 | B-o-n-f-e-r-r-o-n-i 62:8 back 16:2,5 30:2 31:18 41:20 44:8 63:5 80:16 92:8 108:19 114:5 118:3 121:4 133:11 136:5 139:14 141:6,16 153:3 159:17 167:16 background 17:20,23 18:11 BAK 27:16,25 28:4,9 30:13 31:3 ballpark 137:6 152:21 bar 56:12 90:12 bars 93:8 basal 42:11,16,19 43:9,15,20 45:7,15,22 46:4,20,25 47:17 58:15 64:22 74:17, 21 81:8,13,14,22 82:2,4, 10,16,17,23 83:5,6,11, 17,19,24 84:4,5,11,16 85:1,10,12,23 86:4,6,13, 19,20 104:10 114:14 base 87:8 94:12 based 64:24 70:5 94:12 102:23 108:12,15 109:22 111:12 115:7 139:6 152:10 156:18 157:14 baseline 55:4 58:1 60:8 64:3,8 74:6 75:9,20 76:3 78:7 79:5,13 89:20,23 90:14 97:18 98:3,10 107:24 108:7,9,14 163:15 bases 15:20 basic 22:19 28:14 155:22 basically 39:19 53:17 54:7,15 62:9 86:15 160:23 | basis 8:17 15:18 63:6 116:9 bathes 132:8 beans 62:14,18 bear 59:6,9 100:11 begins 73:21 behave 151:3 belated 133:9 believe 7:16 9:4,6 11:10,24 26:1 28:5 29:9 30:9 32:16 35:1 37:22 55:6 80:3 91:20 95:1 108:4 114:5 128:3,8 130:8 135:11 142:7 143:17 144:21 157:21 160:4,16 164:22 believed 160:25 beneficial 145:19 best 8:25 13:22 14:17 17:1 22:2,13 24:7,10 25:19 26:6,11 36:23 39:11 40:18 48:8 77:11 78:13 94:3 106:4,5,11 107:14 121:18 better 8:8 42:5 54:24 56:15 72:13 84:19 93:14 109:9 115:10,16 116:8 137:10 big 58:5 91:10 96:19 120:24 149:17 165:9 big-time 137:2 bioavailability 28:18 156:18 158:15 biostatisticians 95:15 | bit 8:3 65:16 98:6 100:12 117:4,11 140:11 black 52:15 154:10,17,23 blaming 106:25 blanket 79:1 123:9 blepharitis 83:2 Bloch 20:13 32:13 36:10,14,20 37:14 57:17 92:23 93:1,3 95:14 96:6,16 110:12 158:22 164:1 Bloch's 20:18 71:19,24 94:19 95:2 108:12,15 blood 63:4 121:16,17 126:1 127:9 131:6 135:9 137:12 138:18 140:18 149:3 152:15 bloodstream 127:1,3 149:22 blue 54:2 blurred 76:4,7,21 78:8,10,12,23 79:20 81:20 blurry 77:7,8 Board 11:25 bodies 39:9 129:12 body 88:4 130:13 131:3 132:8, 9,13 bold 125:1 Bonferroni 62:7 121:5,12,25 book 18:5 |
|--|--|---|--|

| | | | |
|--|---|---|--|
| bothered 59:7 bottom 41:4 104:25 110:3 169:12 boundary 103:16 break 8:16,17,21 44:6 80:13 109:1 153:1 159:15 168:6 breaks 159:1 brief 12:25 88:24 168:25 bright 167:12 Brimonidine 27:23 28:2 30:4,20 broad 21:20 30:15 41:14 60:5 93:19 94:9,14 123:9 brother 18:25 19:5 brought 71:17 103:23 109:3 159:4,9 bullet 169:11 bunch 63:2 77:3 109:25 146:24 burning 76:20 83:20,23 business 7:12 <hr/> <p style="text-align: center;">C</p> <hr/> C-h-o-r-i-o-r-e-t-i-n-i-t-i-s 130:21 C-h-o-r-o-i-d 130:14 C-h-o-r-o-i-d-i-t-i-s 130:20 | C-i-l-i-a-r-y 129:12 130:14 calculation 63:13,14 California 7:15 call 32:21 53:25 130:19,23 called 11:16,24 17:24 18:5 24:17 25:6 50:12,16 62:7 Calman 7:3,11,13 14:1 16:13 31:18 42:9 44:11 46:14 49:5,24 80:12 89:9 108:19 113:5 124:22 125:14 127:12 133:11 143:11 151:5 155:13 159:22 167:18,23 168:4 169:6 can't 12:10 13:8 45:21 58:6 87:12 91:18,20 94:6,10 102:23 103:1,17 105:21 106:24 111:7 122:20 149:14 cancer 62:15,17,18 capacity 47:21 163:10 capsulized 58:6 care 38:15 96:12 98:5 99:5 career 20:25 careful 68:4,13 87:15 104:8 169:18 case 9:3,8,25 10:5,14,17 11:3, 13 13:10,21 20:16,19 24:18 34:15 35:3,15,18, 25 36:3,8,11,16,20 37:2 39:6 63:9 68:6,9,21 94:20 95:1 102:4 136:8, 10 150:7 166:10 169:20 cases | 14:5 19:2,10,11 21:3 31:14 36:17 38:25 39:4 78:24 castor 51:17 52:4 74:25 156:17 categories 60:6 101:22 104:21 126:16 categorization 101:20 categorized 57:16 58:24 60:4 65:23 66:1 67:1,12 68:1,2,19 73:25 74:19 91:22 92:16 98:23 101:10,25 102:21 105:1,9,15,21 106:13 163:20,22 category 21:20 44:3 60:11 74:17 100:19,21,24 101:2,5 103:15,19 111:17 cause 79:20,21 caused 18:21 78:11 causes 104:6 cautious 68:22 caveat 24:1 47:3 caveats 45:18 47:2 56:6 110:16 114:16 cells 131:6 150:10 center 150:17 certain 22:21 29:14 91:7 96:7 145:14 162:12 certainly 24:3 25:23 28:10,12 34:10 77:15 78:11 117:24 145:13 157:18 cetera 22:24 | challenge 11:21 18:6 chamber 131:7 chance 62:12 63:7 121:10 change 17:3 57:25 58:1 60:15 65:20 72:8,11 76:3 78:7, 8 79:5,13 91:9 92:12,16 96:10 98:3 103:18 105:1, 8,15,19,21,25 106:13 109:8,23 111:17 117:1,4, 8,13,15 120:2 166:10,23 changed 17:4 changes 16:24 60:6,7 62:12 65:19 72:9,24 78:4 91:7,10 98:24 99:7 103:7 107:21 164:15,16 changing 16:2 90:13 chapter 91:18 characteristics 143:14 chart 90:12 100:12 choosing 26:21 61:19,21 chorioretinitis 130:21 137:1 choroid 130:14 132:12 choroiditis 130:20 chose 77:2 chronic 144:8 ciliary 129:11,12 130:13 131:2 132:8,9,12 circulating 155:11 |
|--|---|---|--|

| | | | |
|--|---|---|---|
| citation 133:21 cite 87:14 88:14 92:23 116:14 127:19,21 128:2 168:11 169:14 cited 93:15 103:25 170:2 cites 132:16 141:19 citing 147:4 claim 40:3 70:23 165:25 166:4, 8 claims 40:7 clarify 75:16 classification 90:22 clean 159:11 clear 66:12 67:3 71:11 105:20 116:1 151:15 154:7 clearly 69:13 138:24 clinic 77:11 clinical 21:1,2,13 22:18,23 25:24,25 26:8,14 27:10 28:14 29:3 30:2 44:16 54:5 61:25 96:17 106:6 107:16 115:9,14 116:7 123:13 142:17 155:23 156:11 157:23 158:11,16 161:4 162:3,15,18 164:10 165:5 clinically 47:7 60:7 73:2 91:11 96:20 109:23 113:20,25 115:2 117:12 118:9 clinician 19:25 103:20 157:24 158:16 | clinician's 42:3 clinicians 45:11 56:3 67:2 75:15 clock 162:7 close 31:6 43:12 124:5 closely 73:7 co-authors 64:18 cobalt 54:2 collaborated 15:2 24:6 collaboration 14:25 collagen 137:24 139:18 collateral 122:10 collected 75:15 collectively 30:16 colloquially 130:25 colors 53:21 62:14 column 50:16 107:24 128:9 134:21,24 144:4 152:1 combination 122:19 combine 146:24 come 20:12 34:21 41:20 62:11, 21 63:5 92:24 110:18 comes 121:4 129:5 167:16 comfortable 95:23 107:3,20 | coming 90:21 comments 8:1 commercial 24:13 common 47:7 83:1,14 84:1 90:24 communicate 139:15 communication 68:17 communications 15:22 comparable 136:21 142:25 152:19 161:5 compare 96:23 97:5 102:17 compared 57:11 58:1 63:9 152:14 155:10 163:8 comparing 121:20 165:14 comparison 152:17 158:20 complains 166:25 complete 12:11 17:25 22:3 26:5 110:23 completely 55:2 complex 106:9 component 29:10 components 27:4 52:11 compound 139:4 compounded 24:14,15 25:3 compounding 24:18 25:13 | comprised 130:13 comprising 30:18 concentrate 150:1 152:13 concentrating 150:5,22 concentration 53:21 135:22 136:15 139:2,8 140:12 145:5,11 146:19 148:4 150:21 152:13 154:3,13,14,20 162:4,10 concentrations 128:14 139:7 142:18 150:11 159:25 160:5,11 161:1,3 concept 42:1,3 62:6,7 concern 27:15 31:3 conclude 109:22 concluded 109:7 123:22 concluding 74:3 90:13 conclusion 70:4 73:15 75:2,19 94:12 96:10 122:11 149:23 conclusions 96:14 116:10,11 117:5, 25 137:8,13 142:2 148:9 154:9 conclusive 71:9 concrete 43:22 condition 25:6 31:5 41:19 47:24 103:16 114:25 130:8,10 145:8,9 151:1 161:2 conditions 25:9 30:15 40:14 54:10, 11 83:2,15 84:2,14 162:8 |
|--|---|---|---|

| | | | |
|--|--|--|--|
| conference 107:5,7 | construction 40:3,12,24 41:2,12 165:25 166:4,8 | copy 71:23 80:4 | couldn't 61:2 91:14 107:12 138:6 |
| confidential 15:22 157:6 | construed 40:6 | cornea 54:1,4,9 129:21 145:16 147:8 | counsel 12:16,18 13:15 15:1,2,6, 8,23 16:6,9 71:4 99:18, 20 158:25 162:20 168:4 |
| confining 119:1 | contents 15:21 | corneal 25:5 53:10,13,15 54:8,16 55:9 81:4 90:19 125:4 | count 20:25 |
| conflating 109:24 139:9 | context 55:20 57:15 58:13 60:22 62:24,25 63:17 65:6 72:20 78:2 96:17 97:11 106:6 110:7 125:11 157:23 158:11 162:18 164:10 | corners 154:10,18,24 | country 107:12 |
| confusion 41:15 166:14 170:1 | continue 47:20 | correct 9:13 17:13 18:19,20 23:15,23 38:13,16,20 39:1 40:22 46:18 47:19, 25 55:6 56:2 57:12 58:10 65:23 66:15 73:17 94:20, 23 100:19 101:12 105:5 106:1 108:16 109:23 111:13,14 114:7 116:17 118:6,15,23 122:25 123:2 124:18 127:13,20 128:1 131:22 132:1 155:15 164:25 | couple 17:21 18:22 23:4,8,11 32:11 39:3 137:14 158:23 159:22 167:24 |
| conjunction 35:14,24 36:15 | continuing 18:3 | corrected 77:11 | course 12:5,9 17:24,25 60:2 91:12 94:17 |
| conjunctiva 81:11 125:5 | contrast 57:20 162:8 | correction 62:8 121:5 | courses 18:4 21:4,5 |
| conjunctival 81:6 | control 128:15,24 130:1 141:18 149:2 | corrections 62:9 121:11 | court 9:11 11:23 13:11 34:15, 24 36:16 37:2 38:25 39:6 68:6,8 169:20 |
| conjunctivitis 25:7 | controlled 117:24 | correctly 16:9 23:21 31:1 52:19 121:25 | courtroom 12:7 |
| connection 9:10 20:15,19 23:7 36:11 39:1 81:4 124:17,19 | controls 165:8 | correlate 82:15 83:5 84:3 85:9 86:4 114:24 | create 8:11 |
| Consequently 74:4 | convenient 62:3 | correlated 120:17 142:10 161:4,6 | creates 60:21 |
| conservative 122:7 | conversation 36:15 | correlation 81:13 82:2 83:17 84:15 86:18 101:24 102:9,13 122:18 142:16 155:6 | criterion 121:18 |
| consider 19:16,18,20 20:21 22:14 39:11 44:2,3 117:12 121:17 155:14 | conversations 99:19 | correspondence 124:13 | criticizing 106:4 |
| considerations 27:21 70:9 | conversion 91:3,16 107:18 | corresponding 164:17 | cross-check 110:22 |
| considered 39:10 41:6 68:10,19 69:11 80:23 88:13,15 135:4 141:11 | conversions 89:19,22,24 90:14 97:14, 15,19 103:2 | cosignatories 38:10 | Csa 51:2,5 55:10,12,16 61:10 72:10,13 74:5 75:19 92:14,15,18 109:10 110:25 115:16 116:15, 16,24,25 125:4 126:1 144:5,8,16 145:5,11,19 146:1,20 147:16 148:4, 14 154:14,20 158:4 160:11 163:7,8 |
| consist 52:12 | convert 90:15 | | CSI 154:3 |
| consistency 150:16 | converting 90:16 | | |
| consistent 29:21 46:23 | convinced 152:22 153:7 | | |
| constantly 90:21 | copies 159:11 | | |
| constellation 30:15 | | | |

| | |
|---|--|
| curative 40:13 41:1,13,17 166:15, 18 167:1,13,14 cure 62:18 167:1 cured 41:19 166:18 curing 62:17 current 7:12 currently 9:11 67:10 custom 24:20 cutoff 121:7 cutoffs 90:23 CV 16:19 21:17 26:1 71:20 cyclosporin 23:25 24:4,12 30:8 50:9, 21,24 75:9 125:17,23 126:8 131:20,21,25 135:3,22 136:12,15 137:12,22 138:7 139:2 140:13 141:11 142:3,7 145:14 146:5 147:1,7 150:1,4,9,11 151:1 152:14,18 155:10 159:25 161:6 164:4 cyclosporine 25:17 <hr/> D <hr/> D-e-n-u-d-e-d 54:4 daily 79:6,14 data 20:10 55:2 59:4,6,11 60:18,21 61:23 62:10,24 64:15 65:11 66:2,11,12 67:25 68:15 69:5 70:22 71:9 74:12,14 75:3,4,13, 14 89:25 90:3,10 91:6, 12,14 93:15 94:18 97:20 98:25 99:1,10,14,25 100:2 102:18,19,20,24 103:13 106:5,8,9,12,16 107:1,6,8,9,13,19 110:18,23 116:2,6,22 117:18 120:12,13,24 124:23 127:6 128:4 142:21 150:14,15 152:23 153:8 161:12 date 16:22 36:6 52:22,24 68:13 69:6,14 71:2,5 87:16 dated 14:9 16:20 day 12:19,21 43:21 76:24 104:18 111:8 162:13 days 76:24 147:10 death 10:5 decide 122:15 decided 101:13 deciding 25:12 decimal 93:17,25 95:2 decision 32:7 88:5 decisions 32:10 40:16 declaration 12:17 14:4,11,15,19,23 20:19 29:1 31:18 33:6 34:12 37:6 39:25 41:24 42:10 44:22 46:13 47:11 69:12 70:3 71:12,19,20, 23,25 72:3 76:17 80:12, 20 89:9 94:25 96:3,22 113:5 116:5,21 124:17, 20,22 133:5 156:15,22 157:1 158:19 160:22 167:19 169:7 170:3 declarations 13:10 32:8,12 35:2 37:5, 10,12,13,19,20 39:1 57:18 70:17,21 115:8 133:9 168:20 decrease 58:25 59:8 60:12,13 101:24 102:8 111:4 decreased 78:23 decreases 64:22 deeply 107:7 defects 53:25 defer 98:18 158:14 deferring 157:18 158:2 defined 85:6 definite 69:20 definitely 26:23 27:11 definition 166:12 definitive 69:10 degree 20:2 95:21 96:7 149:11 degrees 19:23 Delaware 10:19 delivered 125:4 delivery 28:18 demonstrate 41:8 163:6 demonstrated 66:18 73:8 119:17 123:23 demonstrates 92:12 denied 100:2 denuded 54:4 department 26:14 depend 93:20 117:2 166:12 depending 53:21,22 136:13 depends 25:22 27:6 39:7 48:5 depicts 72:7 deposed 7:16 8:23 11:3 deposition 11:15 12:14 13:15,18 111:10 168:10,21 169:15 170:14 depositions 9:2,9,20 169:19 describe 9:1 15:14 40:5 51:11,22 described 51:9 123:1 157:15 describes 50:8,19 118:12 describing 50:7 87:8 125:25 description 92:11 123:4 design 77:13,20 156:13 designed 117:23 120:10 147:12,15 148:6,8 despite 109:20 detail 33:9 34:1 85:6 119:13 121:6 detailed 27:3 123:4 | |
|---|--|

| | | | |
|--|--|--|--|
| details 158:12 determine 46:1 77:11 88:7 92:21 93:2,4 95:21 102:17 103:7 105:25 123:14 determining 103:10 developed 26:22 developing 23:24 development 25:17,20,23 27:5 30:20 deviation 72:12 73:9 93:8 109:9,16 110:2,14 Devine 12:25 15:10 devitalized 53:24 54:3 81:10 didn't 11:3 17:25 26:24 36:2 50:23 52:24 61:2 99:10, 25 100:3 105:24 106:23 113:22 121:5 124:16 132:11 168:9 difference 56:16,17 57:6 58:3 59:20 61:9 72:23 96:18,19,20 98:1,10 103:20 110:9,13, 18 111:5,16 114:9 116:3 138:23 140:2 141:4,5 149:5,18 155:9 163:24 164:3 differences 64:11,12 89:20,23 90:3, 14 96:8,10 97:16 98:23 103:3,11 163:12 164:5 different 33:8,10 36:17 39:8,9,18 43:4 50:9 53:21 59:12 60:24 62:14 65:17 66:10, 11,24,25 90:17 97:22 98:13 121:19,21 126:19, 20,24,25 127:2 140:25 146:24 149:6,16,18 151:25 152:3 160:6 161:8,22 | differently 48:22 115:11,16 116:8 151:4 difficult 59:13 104:22 digit 95:11 digits 95:5,12 96:13 Dinning 133:13 direct 79:14,16,23 81:14 82:4, 10,17,23 83:6,11,18,24 84:5,10,16 85:1,12,23 86:5,12,20 direction 150:23 directly 22:7 27:23 34:17 54:21 77:21 81:7 93:15 149:14 162:25 disagree 50:24 73:11 106:3 132:2 disagreeing 73:16 disavowed 80:4 disclose 15:19,21 59:5 160:11 disclosed 80:24 discloses 148:19 disclosing 28:13 disconnect 101:21 discrimination 9:25 discuss 56:7 148:11 157:22 168:4 169:24 discussed 29:1 44:22 46:24 57:17 113:7 114:16 131:19 | 143:13 156:10 158:21,22 169:23 discussing 136:22 160:24 discussion 26:17,18 29:7 36:21 37:1 70:8 124:23 164:15 discussions 25:15 26:13 27:1,4 28:11,15 36:19,24 77:16, 19 disease 76:8 85:19,23,25 137:2 144:1 147:13,23 149:2 151:25 155:8 156:2 161:19,23 166:18 disease/kcs 72:9 diseases 143:23 165:10 disorders 146:2 147:17 disparate 158:20 disparities 75:17 dissolve 137:21 138:6 dissolved 139:19 distinction 101:16 distinguish 45:14,21 46:3 distribute 62:15 district 9:10 34:14,24 36:16 37:2 38:25 39:6 68:6,8,21 169:20 divide 121:14,23 122:1 Doc 77:7,8 doctor 42:2 63:3 99:12 128:18 | doctors 90:15 98:21 158:14 document 13:25 49:10 50:1 88:24, 25 119:9 123:3 125:12, 13,16 127:11,14 134:12 154:10,18,24 documents 12:15 13:6,11 31:23 32:1,3,21,25 34:3,7,8,10, 22 35:4,7,12 38:1 66:13 67:15 68:8 71:17,18 159:4,7,8,9 doesn't 41:20 48:12,13 51:16 62:22,23,24 64:23 67:12 74:11 89:1 96:17 98:8 103:18 147:11,19 148:8, 10 151:3 153:12,14,20 154:11,13 dogs 144:7 doing 22:19 68:22 77:16 106:5 121:16,18 122:9 don't 8:6 10:20 11:2 14:20 16:10 19:16,18,20 23:1, 10 24:6 25:8,10,15 27:11,22 28:11,16 29:24 30:9,22 37:22 38:1,7,11, 14,17,21,23 52:3 60:19, 20,21 61:14 66:6,8 67:24 69:17,20 73:9,13,14,16 74:12 75:11 77:17 80:15 89:6 91:20 93:12 96:3,12 98:5 99:5,14,23 102:15 106:7 107:2,19 109:2 110:23 117:4 118:17 119:9 123:10 124:13 134:11,18 143:10,21 144:21,23,24 151:10 152:6 155:14 156:25 157:9 164:8 166:20 167:2,11 dosage 136:8,11 137:11 dose 136:23 162:13 doses 131:10 161:25 162:1 |
|--|--|--|--|

| | | | |
|---|---|--|---|
| double 126:16 | 131:11 165:11 | effective 42:2,4 88:8 127:25 135:3 136:2,4 141:10 148:17 160:12 162:11 165:6 | emulsion 50:20 51:6 156:18 158:5 |
| double-check 55:7 66:5 67:17 | dry 19:8 22:6 29:3,9 30:11, 16 31:5,9 40:13 41:6 47:24 54:9 72:8 76:8 81:10 82:1 83:1,14 84:1 86:3,17 145:6,8,12,15,21 146:20 147:23 148:1,5,8, 9,11,15,23 153:17,21,25 154:5,16,22 166:25 | effectiveness 142:10,17 | emulsion-treated 67:7 |
| downstream 167:6,7,8 | | effects 60:8 | emulsions 50:9 52:5 57:24,25 |
| dozen 78:2 | | efficacy 41:8 59:12 81:1 88:18,20 123:15 125:7 135:25 146:1 152:9,25 153:9 158:16 161:4,6 162:20, 25 163:4 166:5 | encompasses 40:12 |
| Dr 7:13 14:1 16:13 20:13,18 31:18 32:12 33:2,6 36:7, 10,14,20,22 37:6,14 42:9 44:11 46:14 49:5,24 57:17 69:24 70:3 71:12, 19,24 72:3,16 73:11 80:12 89:9 93:3 94:19 95:2,14 96:6,16 103:21 108:12,15,19,20,22 109:7 110:12,24 111:9 113:5 124:22,23 125:14 127:12,16 133:4,11 143:11 151:5 155:13 156:14 157:5,15,18,20 158:2,21,22 159:22 164:1 167:18,23 168:4, 10,15,16,19,20,22 169:6 | drying 167:8 | effort 27:8 31:10 | encompassing 40:25 |
| | dryness 76:21 81:21,23 114:19 | eight 12:21 | encountered 34:23 |
| | due 66:22 119:5 142:4 | either 56:22 64:18 69:12,13 73:1 96:5 110:13 122:10 130:25 138:22 139:20 140:22,23 142:19 149:20 150:23 162:9 | encouraged 19:6 |
| | duly 7:4 | elderly 31:8 | engaged 10:15 |
| | dye 53:20 | elected 19:4 | enroll 18:1 |
| | <hr/> E <hr/> | electronic 14:7 | enrolled 17:24 |
| | E-p-i-t-h-e-l-i-u-m 54:16 | eliminate 27:16,25 | entered 135:4 141:11 |
| draft 14:23 16:5 | E-x-u-d-a-t-i-o-n 131:7 | eliminating 30:13 | entire 33:18 59:11 115:21 164:14 |
| drafted 23:14 | earlier 10:25 28:6,15 34:14 65:22 109:6 113:7 114:17 124:16 138:11 155:13 156:10 159:5 161:18 162:19 164:22 165:24 168:9 169:25 | emergency 131:13 | entities 30:16 47:9 162:3 |
| drafting 14:19 15:14 16:1,6 | early 14:16 159:24 | eminent 95:15 | entitled 31:20 |
| drafts 16:2,10 | easier 91:13 | emotional 44:1 | envision 114:12 |
| dramatically 126:24 149:20,21 | EAU 136:24 | emphasize 77:2 | epidemiology 21:5 |
| drop 10:11 45:4 48:14 104:4, 5,13 162:14 | education 18:3 19:24 20:24 22:20 155:25 | employ 29:4 123:16 | epithelial 53:25 |
| drops 48:15 142:7 161:24 | effect 11:10 62:17 67:5 74:25 109:21 123:25 142:6 150:12 155:8,21 162:15 | employment 9:25 | epithelium 54:8,16 |
| drug 10:8,10 11:14 24:20 48:2,7,12,17,25 88:7 114:15 156:1,2 165:6,21, 23 | | | equals 55:13,15 56:5 59:19 61:8,11 |
| drugs 26:15 28:19 30:6 31:13 49:2 67:11 123:8,15 | | | equate 98:2 105:2,16 106:14 |
| | | | equations 158:13 |

| | | | |
|---|--|--|---|
| error 80:5 93:8 96:5,6 108:18 escaping 27:18 especially 60:5,6 64:16 91:5 103:21 essentially 138:23 140:7,9 establish 154:8 estimate 14:21 96:7 et 22:24 et al 9:5 132:21 EUA 161:7 evaluated 115:17 evaluating 121:19 evaluation 76:23 everybody 109:16 evidence 87:18 115:9,15 116:7,14, 23 122:10 155:4 evidence-based 21:5 exact 30:22 exactly 31:6 49:15 64:19 77:17 80:10 99:23 109:12 124:4 128:17 138:17 exaggeration 120:25 EXAMINATION 7:7 159:20 168:2 169:4 examined 7:4 example 30:4 32:6 41:23 60:10 | 74:12 90:18 128:4 149:24 161:1,2,21,23 164:12 examples 41:24 92:6 162:3,11 exceptions 165:10 exchanged 16:5 excipient 27:15 excipients 26:19 27:4,9 156:5,12 excluded 166:9 excuse 10:15 56:1 59:17 64:2 78:7 92:17 126:5 143:17 155:2 exhaustive 31:25 34:20 exhibit 13:24 16:13,15 21:25 39:23,24 49:6,24 71:14, 24 72:1 80:20 86:23 113:8,14 125:12 127:12 131:14 133:1,4,6 134:2 168:11 exhibited 70:23 exhibits 31:20 87:17,18 115:8 116:5 168:9 exist 118:2 expect 109:4 120:17 150:2,10 156:16 157:14 experience 19:24 22:20 84:15 85:9 86:3,18 104:1,11 106:11 155:24 164:20 experienced 92:13 experiencing 92:15 | experimental 136:24 143:19 148:7 expert 19:1,9,16,18,20 20:3,6, 21 21:3,9 22:15 23:2 155:14 156:8 157:19 expertise 19:23 21:6 23:1 95:20 123:8 156:6 experts 64:19 158:9 167:12 explain 17:22 29:5 58:21 61:1,3 74:11,22,24 121:5 explained 63:1 64:17 65:4 151:14 152:8 explanation 151:11,16 explicitly 34:11 51:14,18,21 52:3, 14 145:22 147:15 148:10 153:18,22 154:1,11 160:11 explore 19:6 exposed 34:13 exposure 18:24 19:5 express 69:21 140:12 148:21 expressed 47:2 167:19 expressing 71:9 expression 76:19 86:8 extent 29:23 43:3 94:24 95:25 external 146:2 extremely 122:18 148:1 exudation 131:6 | eye 10:11 22:6 29:3,9 30:11, 16 31:5,9 40:13 43:7 45:4 47:24 48:14,15 53:20 54:10,11 72:8 76:8 82:14 83:1,14 84:1 86:3, 17 104:4,5,13 129:22,23 130:18 131:4 138:8 139:13,15 142:13 145:6, 8,12,15,21 146:20 147:23 148:1,5,8,9,11,15 151:3 152:10,12 153:17, 21,25 154:5,16,22 163:10 166:25 eye/kcs 41:6 eyeball 92:24 Eyecare 21:10 eyes 77:7,8 81:10 82:1 148:22,23 <hr/> F <hr/> F-l-u-o-r-e-s-c-e-i-n 53:17 facial 76:19 86:7,11,14 facilitate 30:13 fact 46:12 52:4 58:8 63:1 71:2 102:3 107:7 116:14 121:10 126:4 132:8 135:18 136:5 169:23 factor 121:24 factors 43:22 78:12 93:20 factually 56:2 72:19 failure 87:19 fair 18:17 107:2 115:20 |
|---|--|--|---|

| | | | |
|---|---|--|---|
| fairly 56:6 85:10 | 33:11,13,14,16,18,20 | focus 28:1 30:19 31:11 47:12 158:18 | 19:8 34:24 54:23 136:1 145:19 150:13 |
| familiar 50:1 127:14 | filed 14:12 23:5 33:7 37:5,6, 24 38:2 39:1 | focused 98:3 | Foundation 20:14 69:7 98:15 99:15 100:4 |
| Famy 38:15 | files 124:17 | follow 18:14 39:19 | four 58:19 60:24 154:10,18, 24 |
| far 49:2 63:19 77:4 127:6 150:12 157:19 | filing 23:4 37:4,12,19 38:14 | follow-up 55:5 167:25 | four-month 64:6 |
| fast 8:2 | filings 35:12,20 | follow-ups 158:23 | frame 10:23 70:13 |
| favor 116:3,4 | fills 129:21 | follows 7:5 | frames 77:24 |
| FDA 35:11,20 48:2,17 49:11, 14 65:25 66:7,9,17 67:19,25 68:8,16,17 71:20 77:20,21 86:25 87:6,12,23 88:4,10,20 89:7 110:24 114:2 118:12 122:24 123:5,8, 12,19,22 124:9,12,16 165:4,12,22 | final 170:9 | foreign 107:12 | framework 70:1 |
| feel 36:2 42:4 82:1 100:3 107:3 | finally 86:7 | form 19:19 35:13,22 36:3 37:8,15 42:11 44:2 48:4 50:22 51:13 52:6,13 56:24 57:13 58:11 68:3 69:7 75:22 77:25 79:8 87:10 88:22 91:9 100:16 102:14 103:4 106:2 115:24 118:24 120:3 124:3 146:22 147:21 155:16 156:20 157:16 | FRANCIS 170:11 |
| feeling 82:6,10,14 | find 66:15 110:13 128:18 | forming 18:9,13 31:24 34:4 36:7, 10 40:21,23 | Francisco 7:14 17:8 21:11 |
| felt 95:23 | fine 89:5 146:17 | formulated 27:24 | frankly 41:21 96:3 120:19 |
| fewer 115:4 | finish 7:25 | formulation 23:2 25:12,18,21 51:3,6 52:5,8,12 54:23 55:25 57:11 65:13 70:23 77:23 115:10,15,17,23 116:15, 17,24 117:1 118:15 125:4 156:1,5,8,12 163:7,8 | Frederick 7:11 |
| fibers 139:18 | finished 41:20 143:11 | formulations 22:12,16,22 24:4,8 26:9, 16,21 27:5,24 28:2 53:10 64:12 155:15 156:2 | frequency 162:11 |
| field 18:25 157:19 160:25 | firmly 70:5 | formulators 158:14 | frequently 80:2 |
| figure 53:6 55:18 57:10 59:23 64:2 65:1,12 72:7,17 76:2 77:22 79:3 80:5 81:4 89:14 92:12 93:23 96:24,25 97:22 98:14 100:18 102:24 108:17 109:22 169:23,24 | first 7:4 16:4 26:24 45:10 46:6 48:2,7,12,14,17,23 49:14 55:1 58:16 59:24 70:2 81:23 95:4 99:9 104:9 110:6 113:6 114:21 115:25 119:21 121:13 129:7 133:24 134:5,7,21 145:17 147:9 157:4 | forth 16:2,5 165:9 | Friday 170:10 |
| figures 74:15 | fits 122:20 | found | front 12:7 22:14 29:17 38:6 40:16 70:21 129:22 139:13 |
| file | five 63:4 | | Fujikawa 133:13 |
| | flawed 117:15 | | full 107:1 111:17 |
| | fluid 129:21,23 131:22 | | fully 43:5 |
| | fluorescein 53:16,18,19 | | fundamental 103:12 |
| | | | further 159:13 168:24 |

| | | | |
|---|--|--|--|
| furthermore 150:24 152:16 <hr/> <p style="text-align: center;">G</p> <hr/> gel 138:19 139:17 140:21 143:13 gelatinous 139:16,25 141:1 general 7:21 9:19 13:9 17:8 102:10 113:24 114:22 116:7 157:17 165:11 generalized 149:11 generally 9:1,21 11:1 15:15 16:1 23:16 43:25 45:17 79:24 88:5 115:2 125:19,22 Generic 18:6 get all 104:4 getting 45:24 95:5 104:16 give 12:10 14:21 40:15 41:18 69:10 91:18 94:3,6,10 104:14,17 117:24 120:13,18,20 122:20 161:21 given 9:20 41:24 75:7 92:5 107:8 155:25 gives 44:21 giving 12:7 glanced 34:10 gland 42:17,23 145:16 glands 42:21,24 43:1,3,4 glass 93:18 | glaucoma 26:15 30:17 31:3,8,10, 12,13,17 glaucoma-related 30:6 global 76:22 84:22 glow 54:1 go 24:17 31:15 68:20 74:16, 18 80:22 81:1 89:3,8 92:8 108:9,19 114:5 118:19 119:13 136:5 151:10 155:20 goal 27:16,19 122:16 goes 74:20 going 7:22,23 11:22,23 15:17 53:1 60:12,14 62:11,16 63:4 80:13,19 96:25 98:18 99:4 100:6 101:19, 20 104:14,17 121:9,22 122:14,15 132:23 134:9 138:7 140:24 141:1,5 156:21 168:5 good 7:9 43:11 117:18 122:10 155:5 Grace 15:9 gradings 90:22 gram 129:16 136:13,17 138:13,14,17,23 139:22, 23 140:1,5,7,11,17 142:19 147:8,9 grams 139:21 grape 62:18 graph 56:12 73:10 77:3 79:10 80:3 89:18 93:7 94:13 | graphically 56:13 60:18 graphs 94:7 greater 55:10,16,25 61:11 87:7 113:10,19 118:6 120:1 123:24 green 54:1 grittiness 76:21 gritty 82:5,9,14 gross 108:17 ground 7:21 group 55:11,12,17 58:17 59:19 61:8,10,11 63:9 64:3 79:24 92:15,18 98:21 101:18 110:25 119:8,10 135:20 groups 55:11 56:17 58:17 59:20 61:10 92:14 99:2 101:17 163:13 grown 9:16 guess 22:14 25:22 39:7 42:10 93:18 119:7 169:16 guidance 18:14 <hr/> <p style="text-align: center;">H</p> <hr/> half 33:15 106:18 140:20,21 halfway 134:24 hand 16:12 49:5,23 127:11 handed 71:20 | handing 13:23 16:14 hands 75:13 handwritten 159:7 hang 95:4 109:24 happened 70:25 happy 86:16 hard 103:13 104:4 106:20 Hatch-waxman 18:4 19:7 haven't 63:13 73:13 91:19 92:3 137:9 144:20 he's 73:8 head 8:12,13 10:3 12:25 32:5, 15 35:10 40:18 49:15 heading 40:2 hear 52:24 heart 126:15 151:12 152:1,4 heavy 131:10 heavy-duty 131:12 height 93:7 hesitant 93:5 high 11:7 137:12 139:19 142:3 145:14 147:8 148:1,24 150:3 161:25 162:4 high-frequency 161:25 |
|---|--|--|--|

| | | | |
|---|--|---|--|
| high-powered 137:2 161:19 | 139:10,13,14 140:19 | 131:1 | impregnated 53:19 |
| high-tech 19:1 | hundred 47:4 | i.e. 41:19 | impressed 87:23 |
| higher 65:19,20 72:13 73:9 109:9 127:23 136:11,18 149:21 150:11 | hunk 138:8 | idea 14:20 93:14 105:18 157:17 | impression 85:6 |
| highly 47:18 | hypothetical 94:15 118:1 120:4 166:9 | identification 133:2 | impressive 165:16 |
| histories 33:15 | hypothetically 117:19 150:6 | identified 57:23 68:16,17 127:23 | improve 42:5 |
| history 33:11,13,17,19,21 | <hr/> I <hr/> | identify 92:1 154:3,13,20 | improvement 55:4,8,9,16 58:18 72:10 114:25 |
| hoc 122:9 | I'd 40:15 64:14 134:9 156:22 | identifying 54:3,6 | improvements 73:25 |
| Hoffman 36:25 37:21 | I'll 8:7 55:21 65:10 81:5 92:6 100:1 | illuminate 54:2 | include 42:6 50:24 162:11 166:5 169:21 |
| hold 20:3 21:8 23:1 156:7 | I'm 7:22 8:1 13:5,8 15:5,7, 13,16 32:5,7 34:6,17 37:2 38:4 39:24 40:1 47:13 48:23 49:2,4 52:19 54:13 55:8 57:5 59:2,21 60:4 63:12,13,16 67:5,19 68:11 69:1,10 70:16,18 71:9,10 73:6,7,15,16 80:13 86:24 87:5 88:10 90:11 91:2,9,18 95:4,5, 18,25 97:17,22,25 98:3, 9,18,22 99:18 100:6 102:5 103:5,6,8 105:14, 17 107:20 114:11 116:1, 10 119:1 120:5 121:16, 18,19 123:3 127:7 133:13,20,24 138:1 146:12,14 150:6 151:14 152:22 153:7 154:7 157:7 158:16 161:10 164:6,9 166:20 169:17 | immaterial 138:23 | included 16:1 48:17 50:21 163:15 |
| holds 18:25 | | immune 143:24 | includes 42:23 48:25 |
| hope 123:10 | | immunoassay 126:11 | including 21:4 22:22 30:15 48:14 55:3,5 57:8 58:17 76:16, 18 83:2 124:12 131:6 145:15 152:10 156:1,4 163:13 |
| Hospital 17:8,9 | | immunosuppressant 125:18 | incomplete 93:22 94:15 107:9 120:3, 6 |
| hospitals 17:6 | | immunosuppressive 126:9 | incorporate 17:16 34:11 |
| hour 44:5 | | impact 102:2,11 156:17 | increase 29:13,17 42:7 48:2,15 49:1 60:14,23 64:8 66:16 87:24 101:8 103:14 105:10 110:19 111:1,3 113:9,19,24 114:22 117:7,10,14,20 118:11 119:25 120:15 144:14 154:4,15,21 162:25 163:6,14 164:11,18 |
| hourly 8:17 | | imperfect 47:7 104:11,21 | increased 58:23 67:9 78:9,16,23,25 79:15 81:8,22 82:10,23 83:11 84:11 85:1 86:13 114:15 116:15,24 117:3, |
| hours 12:21 14:22 162:7 | | implication 154:17,23 160:17,20 161:10 | |
| huge 141:2 | | implies 78:23 | |
| huh-uhs 8:13 | I've 11:11 18:7 21:21,22 22:17 25:23 34:7 38:1 41:24 47:2 65:3,4,6 68:7, 17 80:8 91:21 92:4 93:12 94:2 104:8 116:6 134:13 143:13 148:19 151:14 152:8 154:6 163:19 166:21 169:19 | imply 109:17 | |
| humans 165:5 | | important 7:24 8:10 27:10 47:23 81:9 82:15 83:25 84:12 101:15 116:9 156:1 | |
| humor 132:6 | | impossible 136:6 | |
| humour 129:15,17,18,20 130:2 131:8,23 132:2,4 137:23 | I-r-i-d-o-c-y-c-l-i-t-i-s | | |

| | | | |
|---|---|---|---|
| <p>6 120:11 144:8</p> <p>increases 48:8,13 49:3 64:21 66:19 110:21 111:5 118:6 119:17 123:23</p> <p>increasing 48:18 153:17,20,24 156:17</p> <p>Index 85:19,23,25</p> <p>indicate 53:13 70:22 110:24 170:4</p> <p>indicated 29:13,17</p> <p>indicates 150:18,25 152:10,11</p> <p>indicating 72:8,9</p> <p>indication 29:16 144:13 149:17 153:12</p> <p>indirect 78:13 155:4</p> <p>individual 101:16 102:3,18,20 105:20 106:17 114:1 116:2 118:10 139:17</p> <p>individualize 29:2,24</p> <p>individuals 29:2</p> <p>induction/ maintenance 126:10</p> <p>ineffective 136:24</p> <p>infallible 124:14</p> <p>infer 89:13 90:14 103:3 106:12</p> <p>inferred 111:13</p> <p>inferring 89:19,22 90:3 97:16</p> | <p>inflammation 29:19 66:23 119:5 129:10 130:11,15 131:2, 4,5,12 132:5,7 161:15,17</p> <p>inflammatory 29:10 161:2,19</p> <p>informally 93:14</p> <p>information 17:18 18:12 39:14,15,20 47:23 68:5,20 69:12,18, 25 70:25 71:1,3,5 87:14, 15 88:4,13 124:12 148:13 154:7 156:3 161:12</p> <p>ingredient 31:2 48:25</p> <p>ingredients 26:20</p> <p>initial 26:17</p> <p>initially 16:8,9</p> <p>injected 135:19</p> <p>injection 135:19,23,25 136:2,4,11, 14,15 138:3</p> <p>injections 142:16</p> <p>injuries 9:22 19:13</p> <p>input 26:9,15 28:3,8</p> <p>inquiry 146:4</p> <p>inside 87:12 88:9 129:23 131:4</p> <p>insignificant 60:7</p> <p>insoluble 138:8 139:4</p> <p>instance 89:17 105:1 107:24 143:1 151:21</p> | <p>instill 53:19</p> <p>instilling 53:18</p> <p>institution 13:12 32:7,10 40:16</p> <p>instruction 15:17</p> <p>instrument 23:18</p> <p>intent 39:18</p> <p>inter 11:20</p> <p>interaction 158:4</p> <p>interest 147:14</p> <p>interested 18:21</p> <p>interesting 18:24 19:8 100:9</p> <p>internal 157:6</p> <p>interpret 56:3,4 67:2 90:10 130:5 161:11</p> <p>interpretation 72:17 74:10 90:12 140:3</p> <p>interpreted 89:23 97:18</p> <p>interpreting 21:7 130:3</p> <p>interrupt 143:10</p> <p>intraocular 128:13,23 129:8 131:21 135:22 136:16 141:17,23 142:4,12,20 143:23 145:5,9 151:1</p> <p>intravitreal 135:19,25 136:11,15,16 138:3 142:16,17</p> <p>introduced 69:15</p> | <p>introduction 146:25</p> <p>invalidity 9:7</p> <p>invention 19:3 23:8,17 70:7</p> <p>investigation 99:8</p> <p>investigations 146:7</p> <p>investigator's 76:22</p> <p>investigators 28:14 77:16 98:21</p> <p>involve 30:5,8,10</p> <p>involved 9:17 15:11,12 23:24 25:16,20,23 27:3,11,12, 23 28:10,15 30:3 39:14 77:13,15,19 93:6 130:22 156:11 166:4</p> <p>involvement 25:11 28:6</p> <p>IPR 11:19 14:4,12 35:18,25 36:20 37:5,7,13,24 38:19 66:3,13 68:11 124:17,19 166:1 168:18,23</p> <p>IPRS 11:16 14:15 33:4,7 37:20 133:5</p> <p>iridocyclitis 131:1</p> <p>iris 129:11,13 130:9,13 131:2 132:8,12 140:13</p> <p>iritis 130:25</p> <p>irrelevant 149:10</p> <p>irritant 43:7,10,16,18,24</p> <p>isn't 30:4 87:6 111:20 141:22</p> |
|---|---|---|---|

| | | | |
|---|---|---|---|
| issue 15:17 27:10 31:3 33:3 58:5 90:24 102:1 124:8 127:9 153:9 158:19 169:22,23 issues 8:24 18:8 74:14 79:9 127:5 128:5 153:10 157:18,22 158:20 it's 8:10 9:7 11:9,21 14:9,21 18:5 19:8 25:8 29:6,15, 17 31:25 41:19 42:14,15 43:20,22 44:5,16,20 46:10 48:6,12,13 53:23 54:3,7,15 56:21 58:5 59:23 60:14,16 61:21,22, 25 62:3,4,5 63:3,21 66:12 67:1,3 72:18 73:8 74:11 79:19,23 81:9,10 82:15 86:25 88:5 91:5 92:4 94:1,2,14,15 96:12 97:13 98:7 99:5 101:15, 25 103:13 104:4,10,11, 20 106:7,18,19,20 111:19 115:2 118:18,20, 22 121:6 124:5 126:7 128:8 129:8,21,23,25 130:10,17 131:12,13,19, 24 132:9 137:24 138:8 139:4,18 140:1,5,7,20,21 141:5 142:23,24 143:13 144:21 145:7 147:13,15 148:7,24 150:19 152:7, 20 161:16 164:19,20 itching 76:20 82:19,22 its 53:21 107:18 133:8 140:23 142:4 146:25 150:16 <hr/> J <hr/> Jacqueline 15:11 Jad 12:24 15:9 jelly 62:13,14,18 | job 8:8 123:11 162:17 journal 96:5 judge 12:8 JULY 7:1 113:1 June 14:9,16 16:20 jury 12:8 <hr/> K <hr/> KANE 7:8 16:3 20:17 35:16 36:1 37:11,18 44:5,10 48:10 51:1,15 52:9,16 57:3 58:7 59:15 65:7 68:24 69:16 76:1 78:6 79:12 80:18 88:16 89:4 99:11,21 100:8,17 102:22 104:24 106:22 108:25 109:5 111:22 113:3 116:12 119:15 122:22 124:7 133:10 134:14 143:15 147:18 148:2 153:2,5 155:19 156:24 158:1 159:13,16 167:24 168:3,24 169:2 170:8 Kaswan 127:16 131:16 133:12, 23,24 141:16 143:18,21 144:3,21 145:10 146:11, 12,14,18 153:23 154:19 155:2 160:10,24 KCS 22:9 29:20 50:10 119:6 144:7 145:24 146:8 147:1,13,16 162:12 166:25 167:6 keep 115:12 keratitis 144:8 162:5 keratoconjunctivitis 145:24 | key 57:22 152:2 156:12 kidney 126:15 150:8 151:12 152:1,4,5 kind 8:14 10:10 17:22 19:8 100:11 122:18 138:19 140:20 147:24 kinds 90:23 137:19 152:24 153:8 know 7:21 8:7,18 10:20 11:2 12:16 21:4 24:6 25:8 27:22 28:10,12 33:10 34:6,17 35:3 38:4,9 43:15,20 45:9 49:13 56:14 61:22 62:2,6,13 64:23,24 65:9,25 67:24 69:24 72:22 73:1,6,9,14, 16 74:13,24 75:1,11,12 77:4,15 78:10 87:20 88:3 90:17 91:6 92:5 93:12 94:4,5,7 95:25 96:3 99:5, 23,24 100:10 102:15 103:8,17,21 104:15,19, 20 106:16 109:2 110:14 111:18 114:12,21 116:3, 20 117:4,19 118:17 119:1,9,11 120:23 122:8 137:8,21 138:2,9 139:4, 12,20,22,24,25 142:11, 21,24 143:21 144:23 147:5,11 149:6 150:18, 24 152:5,17,20,22 154:9 155:22 157:19 158:8 164:8 166:11 169:19 knowledge 12:1 17:1 19:23 20:23 21:18 22:2,19,21 24:7 26:7 39:10 48:9 61:24 70:5 118:1 155:24 161:11 known 30:16 43:5 103:25 119:2 knows 109:16 | <hr/> L <hr/> L-i-g-n-e-o-u-s 25:6 L-o-f-t-s-s-o-n 32:13 lab 20:25 label 29:16 48:7,18 49:3,12 66:10,15,17 67:20 68:18 71:21 86:25 88:24 113:7 114:3 118:4 119:3 123:2, 6 labeled 29:15 labeling 29:22 labs 20:25 22:17,18 lack 101:24 102:8,12 106:25 lacrimal 42:16,20,23,24 43:1,3,4 142:9 145:16 large 88:4 101:16,18,21,23 102:7 103:8,11 128:15 150:14 165:4 larger 139:16 largest 103:14 late 14:16 laundry 88:18 law 19:17,19 lawyer 18:18 23:9,11 lawyers 17:15 18:14 layer 54:9 60:17 |
|---|---|---|---|

| | | | |
|---|--|--|---|
| layers 130:16 leave 65:10 92:6 left 104:13 left-hand 128:9 legal 17:15,19 18:3,15 39:9 69:8,18 70:1,19 71:10 length 57:17 76:17 81:17 lengthy 29:7 let's 15:9 16:12 53:6 55:14 70:14 76:2 79:3 93:21 96:23 100:11,12,14 107:11 108:5 111:22 113:4 125:11 136:5 143:9,22 149:24 150:8 152:2 159:15 level 11:7 56:5,6 121:9,13,23 128:24 129:8 130:1 132:12 135:21 136:19 141:18 147:7 148:14 150:4 152:18 155:6 156:6 levels 127:10 131:20,21,25 135:4,9 136:12,16,19,22 137:12,19 141:11,23,24 142:4,11,12,13 144:14, 15,18,25 145:2,14 146:4 147:2,3,8,14,24,25 148:16 149:2,3,7,10,13, 18,20 151:7,10,17,20,22, 23 152:8,24 153:9 155:6, 10,11 161:6 light 54:2 76:21 161:12 ligneous 25:6 likewise 28:7 limitation 46:10 | limitations 44:21 45:19 46:7,8,11 107:17,18 limited 106:5 line 167:12 liquid 129:17 138:20 139:24 140:18,21,25 143:14 list 17:7 21:23 22:3 26:5 31:20 32:1 33:12 34:18, 22 80:22 88:18 168:9,10 listed 21:17,21 26:1 32:17 34:5,18 82:5 listing 32:20 85:18 liter 148:21 literal 72:18 89:24 91:3 97:19 105:17 107:18 literally 73:3 97:23 literature 34:25 127:24 litigation 9:11 little 8:3 65:16 66:24 98:6 100:12 117:3,11 139:25 140:11 liver 126:15,16 149:25 150:2, 4 151:12 152:1,4,5 loaded 65:16 local 155:5 located 10:17 129:19,20 Loftsson 32:12 156:22 157:5,15, 20 168:15,19 | Loftsson's 156:14 long 12:20 24:11 25:8 30:21 47:4 151:15 long-term 162:10 longer 17:7 look 15:24 16:12,25 17:3 21:23 30:2 35:4,11,20 46:13 50:11 52:2 53:6 54:17 56:12,14 57:9 58:13,14 59:2 62:22 69:22 70:1 73:18 76:2 79:3 86:22 87:2 88:6 92:8 93:21,23 100:12 102:7 107:22 108:4,20 109:21 113:12 118:3 120:9,10 124:16 125:11 126:4 127:18 133:11 135:14 137:15 141:16 144:3 148:6,8,12,22 151:25 152:2 156:25 169:6 looked 108:16 109:6 135:21,24 142:15 143:17 149:16 151:20 looking 32:7 33:9 34:6 54:13 59:21 62:9 66:14,16 69:1 71:12 73:6,7,10 87:22 98:10 101:22 116:4 127:9 128:7 129:1 131:18 141:20 142:19 143:25 146:13,14 147:14 151:12 153:6 looks 88:4 116:2 122:12 126:4 169:24 Loosely 49:22 lot 16:10 34:7 41:15 62:3 66:25 75:24 76:18 77:1 78:11 79:20 93:20 107:23 121:1,8 139:18, 19 140:1 160:21 165:7 166:13 | lots 120:16 138:1 low 114:14 137:22 150:4 162:1,13 low-frequency 162:2 lower 79:25 136:8,14,23 149:21 162:10 lowest 162:14 LU 152:1 lunch 108:25 109:2 111:21,23 luncheon 111:24 lung 152:4 <hr/> M <hr/> M.D. 7:3 magical 152:12 magnified 93:12 magnifying 93:7,17 magnitude 105:18 114:23 main 42:23 major 30:19 155:9 making 22:11,15 75:1 96:6 malpractice 9:22 19:14 manifest 132:7 manifested 131:5 |
|---|--|--|---|

| | | | |
|--|---|---|---|
| manner 41:3 | 23:13 41:18 99:1 101:23 102:4,7,18 111:6 131:2 135:9 | mention 67:12,13 88:20 131:14 145:17 | 25 117:20 118:6 123:24 144:9 164:19 |
| manufacturer 165:21 | meant 31:25 34:20 54:25 57:14 89:19,22 97:15 107:17 | mentioned 10:7 23:3 30:3 38:24 42:9 65:22 132:1 138:12 154:6 | Mills 12:24 15:9,16 20:14 35:13,22 37:8,15 48:4 50:22 51:13 52:6,13 56:24 57:13 58:11 65:2 68:3 69:7 75:22 77:25 79:8 87:10 88:22 98:15 99:15 100:4,16 102:14 103:4 106:2 109:4 111:21 115:24 118:24 120:3 124:3 133:3 143:9 146:22 147:21 153:1 155:16 156:20 157:16 159:15,21 167:23 168:25 169:5 170:7,12 |
| mark 132:23 | measure 46:20,25 49:20 54:12,19 67:2 76:7,9,10,11 77:10 78:8,14 79:15,16,23 81:7,10,14,22 82:4,10 84:25 85:1 93:17,24 121:7,8 122:15 138:15, 18,21 140:16,19,21,23 142:13 162:25 | mentions 113:8 145:23 | mind 41:17 87:12 88:10 103:19 |
| marked 13:24 16:14 49:6,23 71:14 125:12 127:12 133:1 134:1 | measured 47:17,21 57:18,19 58:19 76:12,16 127:1,3,4 139:20 163:11 | met 12:15 | mine 70:1 |
| Markman 9:3,4 | measurement 29:25 44:18 82:17,23 83:6,11,18,24 84:5,11,17 85:12,23 86:6,12,20 | method 102:16 | minimal 147:3 |
| Mary's 17:9 | measurements 94:20 108:12,15 | methodology 93:1 95:18 114:17 117:14 | minimize 27:8 |
| material 88:15 91:11 113:21,25 114:25 115:3 117:12 118:9 140:2 141:5 163:6 164:12,21 | measures 45:7 57:21 58:15 64:9 77:2 78:3 81:2 88:19,21 162:21,25 163:5 | methods 50:13 77:6 81:24 85:7 136:6 138:4 | minority 87:25 88:1 |
| materiality 164:5 | measuring 63:1 76:3 93:7 94:13 140:4 160:5 | microgram 136:4 | minus 92:17 |
| materially 96:13 98:9 | mechanism 149:25 150:9,22 | micrograms 136:10 138:3 148:21 | minute 70:15 144:10 |
| materials 18:2 36:17 50:12 68:7 77:5 81:24 85:7 88:10 116:22 136:5 138:4 | mediated 143:24 | middle 8:18 50:15 59:24 73:20 134:20,24 | minutes 72:21 134:10 |
| matter 9:15,16,17 10:6,7 39:12, 15,16 61:21,22 116:4 125:14 | medical 9:22 19:13 25:1 69:9 107:4,6 | mildly 73:1 | Mischaracterization 98:16 100:5 |
| matters 20:6 31:24 37:23 39:20 | Medications 50:16 | milligrams 130:2 136:7 137:16 138:5,7,24 139:2 | mischaracterizes 98:17 |
| mean 20:3 24:15 25:22 29:5 30:21 39:7 41:16 47:3 48:6,12,13 52:21 62:17 65:18 77:10 78:18,20 91:4,10 98:23 101:19 103:11 106:1 108:16 114:2 116:1 117:2,19,20 130:5,25 136:12 144:17 150:3 151:5 160:19 165:3 | medicine 21:5 90:24 | milliliter 128:23 137:16 138:16,17 139:23,24 140:10,14,25 141:2 | misleading 125:3 |
| meaningful 73:2 113:20,25 115:3 118:9 | meet 12:18 | milliliters 139:21 | misrepresented 146:17 |
| means | meetings 12:23 | millimeter 60:12 105:3,11,16 106:14,18,19 111:6,7,9, 11,12 | missing 158:11 |
| | | millimeters 66:20 67:1 75:14 87:8 96:19 97:2,24 98:2,7,8, 25 99:4,5,6 101:22 103:16,19 104:14,18 106:19,20,21 113:9,20, | Mission 7:14 |

| | | | |
|--|---|--|--|
| <p>ML 128:14,25 129:16 130:2 135:5,13 138:14,22,24 139:2 140:4,19 141:13, 19 142:19 148:20</p> <p>modalities 30:25</p> <p>modality 29:4</p> <p>model 136:25 144:1 147:13 161:7</p> <p>modeling 92:25</p> <p>moderate 29:8 50:10</p> <p>molecular 139:19</p> <p>molecules 139:19</p> <p>moment 161:14</p> <p>monitoring 30:24</p> <p>Month 55:5,12,13,17,23 56:15 57:1,7,8 58:1,8 59:17,18, 25 61:7 92:13 108:9,14 110:20</p> <p>months 36:15 54:22 55:1 56:21 57:10,23 63:10 64:1 65:14 66:21 72:6 74:16, 18,25 119:22 163:16,18</p> <p>morning 7:9 159:5</p> <p>mouth 93:6</p> <p>move 81:5,18</p> <p>multicenter 118:23</p> <p>multiple 99:12</p> <p>Mylan 9:5 13:17,20 38:6,10,12</p> | <p>99:13</p> <p>Mylan's 100:2</p> <hr/> <p>N</p> <hr/> <p>name 7:9 10:21 27:18</p> <p>nanograms 128:14,23,25 129:16 135:5,12 136:13,17 138:13,14,22 140:4,5,7, 13,17,19 141:12,19 142:18 147:7,9 148:20</p> <p>nasal 45:4</p> <p>natural 19:9</p> <p>nature 23:17 24:8 41:1 165:17</p> <p>NDA 35:8 75:13 124:12</p> <p>necessarily 29:24</p> <p>necessary 36:3 154:4,14,20</p> <p>need 8:11,17 70:15 94:5 115:7 150:11 165:8</p> <p>needed 100:3 128:24 141:18 145:6 155:6</p> <p>negative 72:7</p> <p>neither 110:14 157:23</p> <p>never 10:19 23:13,22 26:16</p> <p>new 48:21 70:22,25 71:3 90:21 165:6</p> <p>nods 8:12</p> <p>noninfringement 9:7</p> | <p>nonprescription 48:14,25</p> <p>nonsensical 145:7</p> <p>nonspecific 94:10</p> <p>nos 8:12</p> <p>note 108:23 109:3 110:22 132:16</p> <p>noted 134:22,25 135:2</p> <p>notes 159:6</p> <p>notion 121:4</p> <p>novel 27:17</p> <p>noxious 43:25</p> <p>nuance 115:4</p> <p>number 44:21 51:22,25 64:14,17 65:18,20 71:24 76:23,24 92:25 102:11 109:13 120:21 121:14 122:1</p> <p>numbers 65:5 75:7 92:22 93:4 96:2 101:23 102:7 108:3 164:7,13</p> <p>numeric 78:3 93:15</p> <p>numerical 85:14</p> <p>numerically 56:15,22,25 57:1 65:12, 15 77:23 84:19</p> <p>Nussenblatt 132:20,21 133:13 141:20,22,25 142:2 143:2,18,19 145:4 146:13 147:4 148:3,6 150:24 152:11,16 153:20 154:13 155:3 160:10,23 161:5</p> | <hr/> <p>O</p> <hr/> <p>oath 12:4</p> <p>objection 20:14 35:13,22 37:8,15 48:4 50:22 51:13 52:6,13 56:24 57:13 58:11 65:2 68:3 69:7 75:22 77:25 79:8 87:10 88:22 98:15 99:15 100:4,16 102:14 103:4 106:2 115:24 118:24 120:3 124:3 133:3 146:22 147:21 155:16 156:20 157:16</p> <p>obscure 60:16</p> <p>obtain 17:18 35:5</p> <p>obtained 73:25</p> <p>obviously 12:16 31:13 38:24 39:8 41:20 101:18 108:16 111:2 145:3</p> <p>obviousness 70:5</p> <p>occurred 10:24</p> <p>ocular 19:13 27:9 28:18 30:14, 18 31:16 66:22 81:11 83:2 84:2,14 85:18,22,25 119:5 143:6 145:8,11 146:2,20 148:4,14 154:3, 15,21 161:2,15,23 162:12 167:7</p> <p>odd 58:14</p> <p>Oellerich 148:12,13,16 151:6,21 153:11,14,15,16 154:2</p> <p>offer 70:18</p> <p>offered 31:2 70:20 71:1,3 156:15</p> <p>offering</p> |
|--|---|--|--|

| | | | |
|---|--|--|--|
| 20:5 39:6 157:13 | 154:12,25 155:20 156:9, 14 157:12 158:17,23 159:4,16 160:9 168:14, 24 169:2,8,10,13,16 170:7 | oppose 69:2 | overlap 31:9 36:17 |
| office 11:17 12:2 99:14 | | opposed 45:15 | oversell 103:6 |
| oftentimes 162:5 | | opposing 99:19 167:12 | oversimplification 42:14 114:18 |
| Oh 10:5 113:15 122:12 146:15 | old 71:1 | orange 53:23 | oversimplifications 45:10 |
| oil 24:12 51:17 52:4 74:25 142:7 156:17 158:4 | olive 24:12 142:7 | order 11:9 13:12 46:3 68:7,10 124:10 164:18 | owner 59:4 |
| oily 137:25 139:11 | Omniprep 17:25 | ordered 63:3 | <hr/> P <hr/> |
| okay 7:21 8:4,8,9 9:14,19,23 10:2,6 11:1,15 12:3,10, 22 13:6,14,23 14:6,14, 18,23 16:12 17:10 18:9, 13 20:5,18,21 21:19,23 22:8 23:3,13 24:21 25:2, 11 26:3,25 27:20 28:2,7, 21 29:12 30:2 32:3,20 33:20 34:2 35:9,11,17 36:2,18,21 37:12,19 38:14 39:13,22 40:20,23 42:6,22 43:6,13,19 44:23 45:6,20 47:5,15,20 48:11,16 49:5,13,17,20 50:11 51:2,10,16 52:10, 17 53:6 54:12,22 55:22 56:11 57:4,9 59:16 61:4, 16,19 63:8,19 64:25 65:8 67:21 68:25 71:11,22 73:5,18 74:9 75:18 76:2 77:22 78:7 79:13,17 80:7,22 81:16 84:21 87:1,5,6 88:17 90:2 91:24 92:10,21 93:16,21 94:7,19 95:10 96:15,23 97:5 99:22 100:1,18 101:14 102:11,23 103:1 107:3 108:8 109:14 113:4,15 114:2 115:1 116:13 118:20,21 122:23 123:12,21 124:8,15,21 125:10,11,16,21,25 126:23 127:4,11 129:25 130:7 131:17,24 132:23 134:1,11,20 135:11 137:7,14,20 138:25 141:3,6 143:16 145:1,10 146:17 153:1,6,19 | once 162:13 | orders 32:11 | P 55:11,13,15 59:19 61:8, 11 |
| | one- 64:6 | ordinary 52:21 59:1 60:3 61:15 70:6 156:16 157:14 | P-o-s-a 68:12 69:3 |
| | ones 15:13 27:22 33:8 | organ 125:18,21 126:9 128:22 151:4 | P-u-n-c-t-a-l 67:11 |
| | ongoing 38:25 | original 60:17 | p.m. 111:25 113:1 153:3,4 159:17,18 170:15 |
| | online 18:7 | originate 16:4 | page 14:6 21:24 26:2 31:19 50:11,12 53:7 55:19 65:5 66:17 73:18,21 87:3,5 88:21 89:2 108:6 110:3 114:6 126:5 128:9,19 134:20 135:20 141:6,8, 17 168:12 169:9 |
| | operates 123:5 | OSDI 76:19 | pages 47:4 128:2,4,6 |
| | ophthalmic 22:12,15,22 23:19,25 24:3 25:17,21 27:5 50:20 51:3,5 67:7 155:14 156:2,4 | outcome 81:2,9 | pain 76:22 84:7,10,12 |
| | ophthalmologist 17:12 | outer 54:8 | palliative 40:12 41:1,12 166:5,9, 13,14 167:10 |
| | ophthalmology 24:3 132:22 133:15,22 155:23 | outgrowth 19:9 | pancreas 152:4 |
| | opine 92:4 94:1 | outlier 59:13 62:1 | panel 63:3 |
| | opinion 32:22 69:17,21 70:18,19 71:5,10 94:23 115:21 117:1,9,13,16 120:2 150:16 | outset 34:19 97:12 120:10 122:16 | panuveitis 130:23 |
| | opinions 15:20,21 18:9,13 20:5 31:24 34:4 36:3,8,11 39:4,5 40:21,23 156:15 157:13 166:10 167:19 168:17 | outside 18:10 | paper 50:4,6,8,18 52:15 75:19 80:6 90:18,19 125:25 |
| | | outstanding 8:20 | |
| | | overall 32:23 60:22 85:5,8 117:5 163:10 | |

| | | | |
|---|---|--|---|
| 128:18 131:16 134:15, 17,18 135:12,15 137:9, 13 138:2 141:20 143:6 144:20,21 145:2,17 146:3,25 147:6 160:23, 24 | particularly 60:22 68:16 74:14 147:6 165:10 | 2 92:14,17 101:16,17,18, 23 102:3,4,8,12,18 106:17 111:2 119:4,11 120:20 124:1,2 125:22 126:2 153:17,21,25 154:5,16,22 162:6 | petition 13:12 32:6 38:10,15,17, 21 |
| papers 22:8,11 60:4 90:6,9 91:15,21 92:1 93:10 143:16 | parties 10:12 11:21 41:16 | pediatric 152:5 | petitioners 38:6 133:5 |
| paragraph 39:22 40:5 41:4 46:12,13 47:10 59:24 63:18 70:4, 12 72:2,6 73:20,24 80:11,20 87:13 88:18 89:8,17 92:9 95:8,9 96:24 104:25 107:22 108:20 110:3 113:4,17 115:2,6,7 116:13 123:6 124:21 127:18 129:5 134:25 143:5 144:5,24 145:17,25 156:25 157:7, 9 169:7,14 | parts 16:7,8 34:14 147:5 | peer-reviewed 93:10 | petitions 32:9 37:24 38:2,5,11,12 |
| paragraphs 70:9 | party 38:12 | pending 9:11 11:16 | PH.D. 7:3 |
| parameter 120:11 | pat 75:5 | people 19:7 44:2 62:15 79:21,25 90:21 130:24 | pharmaceutical 22:21 |
| parameters 80:23 84:18 88:7 90:23 120:16 121:8,15,19 122:2 | patent 8:24 9:16,17 11:17,24 12:1 17:25 19:1,17 23:4, 5,9,11,22 33:12,21 40:25 59:4 99:14 133:8 | percent 24:11 50:19,20 51:2,5 55:12,17,24,25 56:22,23 57:10 61:10 65:13 67:6,8 72:11,13 74:15 77:23 84:19,20 85:14 92:15,18 96:9 109:7,10 110:19,20, 24,25 115:10,11,15,16, 22,23 116:15,16,24,25 118:13,16 119:12 120:20,21 124:1,2 140:8 163:7,8 164:4 | pharmacist 24:19 |
| paraphrase 29:16 | patenting 19:4 | perfect 62:5 123:11 | pharmacokinetic 21:7 144:2 147:23 157:6 |
| part 11:25 12:1 17:17 24:25 26:23,24 27:8 50:25 66:15 94:25 96:2 120:8 125:14 129:22 132:9 139:13,14 162:17 170:1 | patents 9:10 11:22 18:22,24,25 33:3,4 40:7 | perform 20:11 29:25 45:13 | pharmacokinetics 20:22 21:9 |
| partes 11:20 | patents' 18:8 | performed 28:17 47:8 84:19 163:18 | pharmacy 24:18,19 25:13 |
| participants 107:13 | pathophysiologic 166:23 | period 13:1 | phase 9:5,8,17 27:11,12 50:8 67:25 77:14,17,20 80:24 118:12 164:24 165:14, 15,20 |
| particular 40:7 59:10 65:21 76:13 88:25 94:21,25 96:2 119:10 127:9 143:25 144:20 149:9 150:19,23 170:3 | pathway 11:21 | permeability 142:5 | Phillips 12:24 15:10 |
| | patient 30:24 41:7 42:4 47:18 54:20 67:13,14 76:23 77:6 82:3,16 83:4,16 84:4,13 85:11 86:1,5,15 100:13,19,21,24 101:2,5, 20 105:21 106:1 114:1, 14,18 118:10,13,16,17 119:24 121:19 166:24 | person 52:21 59:1 60:2 61:15 70:6 95:18 148:25 156:16 157:13 | phone 13:4 |
| | patient's 41:6 42:1,5 47:24 81:25 82:14 85:7 102:20 104:16 114:25 | perspective 69:18 | photophobia 83:7,10,13,17 |
| | patient-reported 76:14 | | phrase 161:18 |
| | patients 24:5 25:3,4 29:8,14,18 30:11,14,17,23 31:4,7 42:11 58:9 66:21 67:7,9, 10 76:8 78:25 79:2 83:1, 14 84:1 86:2 87:25 88:1, | | phrased 48:21 |
| | | | physically 139:1,3 |
| | | | physician 41:8 53:14 |
| | | | physician's 84:21 85:4,5 |
| | | | physiologically 62:23 64:20 |
| | | | picture 165:9 |

| | | | |
|--|---|--|---|
| pictures 29:3 | 57:8,20 58:19 59:8 60:21,24 62:10 64:7 78:5 93:17,25 142:22 | 162:6 | presentation 124:23 125:3 |
| piece 71:8 87:13 88:13 116:2 | poked 12:25 | potential 23:7,17 | presented 74:4 |
| pitfalls 57:16 | poor 142:4,5 | potentially 26:23 73:1 104:17 | presenting 107:4,10,11 |
| pivotal 50:8 164:23 165:2,13,18, 20 | popped 122:13 | practice 17:7,11 22:23 28:22,25 34:13 44:11 49:18 107:16 | preservative 27:17 28:9 |
| PK 124:23 127:22 | population 30:24 31:9 67:14 85:11 86:5 98:24 99:2 105:19 106:1,14 118:14,17,18 119:24 121:21 | practicing 17:12 42:2 | press 11:12,13 |
| place 28:4,9 70:14 99:9 | populations 103:12 | precise 14:20 16:11 40:15 43:14, 15 52:7 92:25 103:9 | presumably 77:9 87:21,23 142:5 |
| places 95:2 | portion 55:22 130:18 | precisely 93:2 | presume 88:14 |
| plan 29:11 | portions 34:1 | precision 95:21 96:7 | presumed 29:19 66:22 119:4 |
| plausible 138:4,5 | POSA 36:5 68:12 69:2,6,13 87:16,22 88:11 119:2 148:25 161:13 | preclinical 27:13 | pretty 21:20 43:11,12 45:24 120:21 123:9 131:12 137:1 |
| plausibly 138:21 | posed 15:19 | predictably 135:3 141:10 | prevent 150:2 |
| please 8:7 31:20 39:23 67:22 73:19 92:9 107:16 141:6 156:23 169:6 | posit 149:8 | prefer 40:15 | preventing 150:12 151:24 160:6,7,8 |
| plot 97:22 | positive 72:9 121:9,22 | preliminary 32:10 | previous 98:18 139:6 |
| plugs 67:11 | possession 34:21 | Premier 21:10 | previously 13:24 16:14 49:6 87:2 93:11 125:12 127:11 134:16 140:15 166:22 |
| plural 37:10 42:21 | possible 139:1 143:23 | premise 95:6 | primarily 128:7 |
| plus 22:18 92:15 98:1 108:9, 14 | possibly 24:25 | preparation 13:15,18 33:17 168:18 169:20 | primary 99:10 |
| point 15:16 27:18 55:2 56:20 57:19,22,23 58:23 59:10, 11,22 64:5,13 65:21 67:22 71:9 74:20 85:13 96:8 99:8 109:15 110:10 122:8 133:7 142:1,25 160:4 163:15 164:4,23 170:5 | post 122:9 | prepare 12:13 | principles 17:15,19 18:15 20:2 156:19 157:15 158:3 |
| pointing 63:23 | post-treatment 98:11 | preparing 17:14 168:16 | prior 12:17 13:13 20:8 127:24 134:18 168:16 |
| points | posterior 129:12,21 130:17 | prescribing 41:7 | priority 36:6 52:22,24 68:12 69:6,14 71:2,5 87:16 |
| | potency 162:14 | prescription 48:7 49:2 | privilege 15:18 |
| | potent | presence 43:16,17 | |
| | | present 12:22 107:6 | |

| | | | |
|---|--|---|--|
| privileges 17:7 privy 99:18 probably 11:11 14:21 30:21,23 39:17 62:16,18,19 63:4 75:2 80:5 92:6 93:13 94:4 109:16 117:8,12,15 134:6 136:3 140:11 166:17 problem 85:11 120:8,23 problems 46:7,8 120:7 167:16 proceeding 34:24 133:7 proceedings 14:12 50:4 166:1 process 15:14 16:1 produce 94:18 142:3 produced 42:16,19,20,25 43:2,4,6, 9,16,17,23 45:15,16,22, 23 product 9:6 10:21 11:13 15:18 23:25 24:13,14,16 25:3 production 29:13,18 30:1 42:7 44:15,17,19 47:1,17,21 48:3,8,13,15,19 49:1,3, 21,22 54:20 64:21,22 66:21 67:9 78:9,13,16, 24,25 79:15,25 80:6 81:8,13,15,22 82:3,4,11 83:12 116:16,25 117:3 119:4 153:17,21,24 154:4,15,21 160:13 163:1,7 products 156:4 professional 21:21 professor 21:14 | professors 24:2 projects 21:1 27:2 properties 138:20 proposition 127:22 proprietary 52:5,8,11 protecting 31:16 protective 11:9 68:6,10 protein 131:6 protocols 28:13 30:22 31:15 prove 121:1 provide 7:24 11:5 54:12,19 78:15 89:25 96:16,17 97:20 148:13 153:12 155:3 158:10 provided 18:14 77:5 106:10 124:11 164:7 provides 41:5 44:18 47:22 providing 107:8 proxies 47:8 proxy 44:16 54:7,15,17 PTAB 11:24 13:11 40:6 69:15 99:20 100:2 PTAB'S 40:11,24 41:2,12 public 11:12 35:20 124:16 publication 94:13 107:11 | publications 21:2,24 22:3,5 94:8 published 22:8,11 24:5 90:6,9 91:17 pulled 144:20 pumps 150:9 punctal 67:11 purpose 71:6 147:15 168:22 put 47:3 55:20 57:15 60:17 65:5 78:1 93:5 104:4,21 106:6 157:22 162:6,17 164:9 putative 89:18,21 91:16 97:14,15 98:1 103:2 putting 63:16 <hr/> Q <hr/> qualified 91:2 157:20,21 quantification 78:15 quantify 44:14 102:2 quantitative 44:18,20 quantities 47:9 question 7:25 8:6,20 15:25 20:9 41:14 48:16,21 53:3 61:4 66:4 68:14 69:9,10 70:11 80:8 94:1,2,10,11,15 95:6,17,22 100:7 102:5 110:4 119:7 120:6 122:21 124:11 132:15 140:9 144:23 145:7 146:10,18 147:12,19 148:13 151:18 157:12 163:4 168:8,14 169:18 | questioning 63:14 questionnaire 86:1 questions 7:23 15:19 53:2,4 75:5 86:2 95:13,19 159:13,23, 25 160:9,14 162:20,24 163:2 165:25 166:3 167:25 168:5,24 170:8 quibble 98:6 99:3 111:18 137:4 142:22 quibbling 96:4 106:4 quick 16:12 86:22 167:24 quite 56:9 89:16 147:6 167:11 quotation 55:19 quote 128:10 129:5 147:4 169:21,22 quote/unquote 74:17 164:17 quoting 34:17 67:5 147:4 <hr/> R <hr/> rabbits 146:5 raises 75:4 random 62:12 63:6 121:9 randomized 118:22 range 97:25 103:16 128:22 135:5 136:20,23 141:12 142:19 143:5 149:5 150:25 155:4 ranges 98:20 126:1,8,20 136:21 142:25 143:1 148:19 |
|---|--|---|--|

| | | | |
|--|---|--|--|
| rapidly 67:19 | recall 10:18,23 13:3,6 14:18 16:9 25:25 28:20 33:1 35:3,10 38:11,14,17,21 42:13 90:8 91:20 109:6, 11,12 113:11,16 121:25 123:20 125:13 156:14 160:2,14 162:22 163:2 165:24 166:3 | 142:1 | relative 87:20 |
| rare 25:6 165:10 | recapitulate 164:14 | reflected 30:23 | relatively 131:10 136:23 |
| rat 138:8 140:10 | recess 111:24 | reflects 104:10 | releases 11:12 |
| rating 76:19 86:8,12,14 | recognize 13:25 16:16 | reflex 44:2 58:16 74:21 104:6 114:13 | relevant 21:21 33:16 34:1 47:18 61:23 86:2 128:4 135:15, 18 145:15 146:5 147:6, 25 148:10 |
| rationale 28:13 | recollection 8:25 13:22 14:17 16:11 22:13 24:10 25:19 26:6, 11 28:16 36:23 40:19 134:16 | reflexive 42:12,25 43:2,6,23 45:8, 16,23 46:4 74:6 75:9,21 104:15 114:15 | relied 17:14 18:10 31:23 32:1 34:4 40:24 65:25 67:25 87:6 94:19,24 |
| rats 137:1,10 142:9 | record 7:10 44:8,9 80:16,17 97:13 153:3,4 159:17,18 | reformulated 27:24 | relief 41:5 |
| raw 59:3,6 64:14 75:3 89:25 91:12,14 97:20 101:25 102:17,20 106:16 107:15,19 110:15,18,23 163:22 | record's 71:11 | refresh 134:15 | relook 120:12 |
| reach 56:9 149:23 | reduce 152:13 | regard 36:20 110:10 136:22 152:14 158:12,14,19 163:17,21 164:5 | reluctant 69:10 70:18 |
| reached 75:19 | refer 127:8 | regarding 41:12 47:23 114:17 158:13,20 159:1 160:10 162:20 165:25 166:4 | rely 32:3 95:3,19 115:9 |
| read 18:5,7 20:1,10 31:15 33:8,25 55:23 60:1,2 61:6,14 65:5 67:2 89:1 97:13 110:4 115:6 128:21 134:5,6,7,10,13, 15,16,18 150:20 157:9 168:15,18,19,21 169:16, 17,19 | reference 32:18 48:18 66:6 67:16, 18 135:12,17 162:21 169:25 | regime 126:10 | relying 34:17 88:10 93:1 95:24 |
| reading 17:20,23 18:10 19:7 55:8 60:3 61:24 70:16 81:24 137:3 152:23 153:8 | referenced 32:17,21 34:18 | reject 61:19 | remain 103:15 |
| ready 111:21 | references 13:13 127:8,19 154:8 160:11,24 | rejection 148:17 150:3,12 160:7,8 161:9 | remains 122:8 |
| really 77:8 94:4 98:8 111:19 120:22 143:4 144:1 | referencing 164:23 | relate 9:21 10:8 11:8 22:5 41:11 143:18 | remarkable 150:15 |
| reanalysis 120:13,24 122:13 | referred 50:4 161:14 | related 8:24 9:9 10:6 11:14 35:12 37:23 68:1 86:17 | remedies 42:6 |
| reason 12:10 95:22 107:10 119:1 169:18 | referring 19:12 118:20,22 129:4 151:6 | relates 11:16 143:19 | remedy 41:5 |
| reasonable 47:8 | refers 66:9 113:6 118:5 133:12 | relating 125:17 | remember 13:8 23:10 25:9,10,15 28:11 30:22 32:16 38:4,7 77:17 |
| | | relation 160:1 | remind 97:12 |
| | | relationship 151:16,24 158:15 | render 149:10 |
| | | | repeat 63:17 152:7 |

| | | | |
|---|---|---|--|
| repeated 62:19 121:3 | resident 24:2,22 | 11:21 32:9 37:6,13,20,24 38:2 115:8 116:5 156:3 | S-m-o-l-i-n 103:24 |
| repeatedly 91:13 110:17 | respect 35:21 53:10 103:1 114:2 156:15 158:3 161:8,19 163:9 | reviewed 12:15,16 13:7,9 20:18 33:13,14,16,18,24 34:7, 12 76:16 89:7 93:11 134:4 | sad 86:16 |
| report 11:5,8 39:25 108:20 110:9 158:7 168:11 | respond 100:7 | reviewing 21:1 32:16 37:23 38:11, 15,17,21 125:13 134:12 | safe 88:7 165:6 |
| reported 56:19 58:8 60:18 64:25 91:23 137:16 143:1 162:21 163:5,23,24 164:24 | response 13:12 32:6 43:7,10,24,25 84:22 85:7 119:12 133:8 | rheumatoid 166:24 167:2,4 | safely 11:11 |
| REPORTER 170:9,13 | responses 32:9,10 | right 7:17 8:14,21 13:23 17:12 26:5 27:20 28:7,17 33:11,23 42:7,18 44:4 47:16,24 49:23 63:15 76:2 80:15,19 89:16 100:14 101:11 102:9 104:14 105:22 110:4 113:21 115:5 118:9 119:23 122:24 124:9 126:17 127:25 132:14 138:25 140:5 141:20 147:20 151:7,22 | safety 123:15 |
| reporting 76:13 91:7,8 108:7 139:7 141:9 | responsible 167:18 | right-hand 50:16 144:4 | Sall 50:3 51:10 52:10 53:5,6 55:19,22 57:9 58:9 59:17,23 61:4 64:18 65:1,11 66:8,25 67:15 71:21 72:7,17 73:18 74:10 79:3 80:24 89:14 90:19 91:21 92:12 93:21, 23 96:24,25 98:13 100:18 102:24 108:4 109:21 115:17 118:19 162:21 163:5,9,23 164:24 |
| reports 39:2 61:5 | responsive 66:4 133:8 146:4 | roles 21:16,20,21 | San 7:14 17:8 21:11 |
| represent 10:14 | rest 61:23 62:24 89:3 | rough 44:16 170:10 | sandiness 76:20 |
| reproducibility 122:11 | restart 167:17 | roughly 136:20 148:19,20 | sandy 82:5,9,13 |
| reproducible 111:7 117:23 | Restasis 9:11 28:21,24 29:12 35:8,12,21 48:1,17 49:4, 12,13 66:1,18 67:6 68:2 86:25 87:19 113:7 118:14 119:16 122:23 123:22 165:14,15 167:14 | rules 7:22 39:8,19 | saw 18:23 19:9 170:4 |
| request 35:4 100:2 | Restasis-treated 87:25 | run 46:4 90:25 | saying 73:16 91:2 97:17,23,25 103:6 107:20 115:12 116:1 150:6,7 165:15 |
| requested 99:18 | result 56:15 58:14 62:20 103:18 | running 45:20 | says 46:10,16 48:7 49:3 52:4, 7 55:14 69:1 70:4 72:6 74:3,4 85:4 90:1 92:11, 20 95:20 105:7,8,12,14 114:3 118:13,19 124:5 125:2 128:16,20,21 129:7,25 130:6 134:21 135:8 136:10 138:5 141:17 144:7 146:19 |
| require 89:25 97:19 161:25 162:1 | resulted 137:11 | S | scale 76:14,19 77:7 78:4 86:8, 12 90:18,20 |
| required 105:10 125:6 145:5,11 146:19 148:4,14,17 149:18 152:8 | results 53:9 64:1 69:5,19 70:24 71:7 74:4 115:22 123:1, 13 137:15 140:24 157:5 | S-j-o-g-r-e-n-'s 145:20 | |
| requires 131:9 165:4 | retest 63:5 | | |
| research 22:19 26:13 28:1 94:5 155:22 156:11 | rethink 117:25 | | |
| researched 165:19 | retrospective 120:12 | | |
| resent 106:7 | review | | |

| | | | |
|---|---|---|---|
| scales 90:17,22 | 25 106:13 107:24 109:8 114:14,23 118:14 120:1, 15 164:18 | 150:12 151:12 156:22 157:4 158:6 167:11 168:13 | 152:7 157:4 |
| schedule 86:14 | scores 65:23 66:1 96:20 97:1 107:15,21 119:18 144:14 | seeing 32:6 67:19 119:20 136:12,16 138:1 | separate 39:4,5,8,12 44:3 |
| schemes 90:22 | se 20:4 21:9 23:2 153:22 154:1 156:8 | seen 11:11 38:1 49:7 54:9 57:25 66:3,4 67:5,6,9 68:7 83:14,15 84:14 87:2 91:15,19,21 113:8 115:9, 14 116:6 123:25 135:20 136:8 | September 127:24 |
| Schiffman 70:17 168:16,20,22 169:15 | searches 34:25 | segregate 39:14 | series 7:23 162:19,24 |
| Schirmer 44:12 45:6,7,13,17,20 46:5,17,24 47:22 49:17 57:16 59:3,16 60:5,10,12 64:2,15 65:23 66:1,19 67:13,17,18 68:1,2,19 72:8,12,24 73:25 74:18, 19 75:3 81:17,18 87:7 91:6 92:13,16 96:19 97:23 98:25 100:14 101:8,10 103:23 104:1 106:13 107:15,21,24 108:6 109:8 110:11 111:8 113:9,18,24 114:14,23 117:20 119:18 120:1,15 123:24 144:9, 14 164:17,18 | second 26:23 46:16 50:11 52:2 63:23 72:5 109:24 113:17 155:12 169:11 | self-assessment 81:25 82:13 | serum 128:23 135:3,8 136:22 141:11,23 142:11 143:2 149:13 150:4,11,25 151:7,9,17,21,23 152:8 155:7,10 161:5 |
| Schirmer's 58:15,21,23 60:22 64:8, 13 67:3 75:8 91:20,22 101:25 104:2,9,12 163:11,17,21 164:6,13 | secondary 70:8 | self-evaluation 86:19 | serving 21:3 |
| school 148:25 | secreted 132:9 | self-rating 86:15 | SESSION 113:1 |
| science 28:14 90:24 91:25 | secretion 46:20 64:10 82:16,18,24 83:5,6,18,19,24 84:4,6, 11,16 85:2,10,12,24 86:4,6,13,19,21 163:10 | self-reported 77:6 | set 56:5 61:23 62:24 66:11 68:15 74:14 75:4 98:20 101:13 106:6,12 107:9, 19 110:23 120:24 150:14,16 |
| scientific 21:1 60:3 61:25 69:9 90:3 | section 40:2 50:12,15 77:6 81:25 89:11 105:13 107:25 128:8 | semantically 48:6 | sets 61:24 |
| scientist 19:25 152:22 153:7 161:11 | sections 33:16 | semantics 20:8 | settled 10:25 |
| scientists 56:4 62:21 90:10,15 | see 15:9 19:15 31:21 33:22 40:2,9 41:9,10 46:21 50:12 52:3 53:11 54:1 55:14 56:15 59:3,10 61:12,13 62:21 63:11,12 64:14 70:3,14 71:17 72:5,14,15 73:23 74:7,8 76:5 79:7 80:25 82:7,20 83:8,21 84:8,23 85:20 86:9 87:4 89:15 92:19,20 96:25 97:3,10 105:4 106:21 108:1,5 111:22 113:12 115:18,19 119:19 124:24 125:1,8,9 126:7, 12,14 129:3 130:4 132:18 133:18,20,21,23, 24 135:6,7,14,20 137:17 141:14,15,16,21,25 143:22 144:11,12,24 | semi-ocular 131:13 | severe 29:8 50:10 136:25 161:2, 15 |
| scope 87:16 | | semisolid 143:12 | severity 47:23 |
| score 60:9 72:12,25 92:13,16 97:6,7,8,23 98:7 100:14 101:9,11 105:2,9,15,21, | | send 170:10 | shaking 8:13 |
| | | sending 16:2 | share 11:11 |
| | | sense 30:12 44:20 60:21 62:23, 25 64:23 | sheet 38:6 |
| | | sensitivity 76:22 | Sheppard 32:12 103:21 111:9 168:10 |
| | | sentence 42:1 46:16 47:3,11 58:6 61:17,20 72:5 74:3 75:11,25 105:8,14 109:6 110:7 113:6,17 119:21 125:2 128:20,21 129:1 131:18 134:21 145:23 | shifting 85:3 |
| | | | short 44:6 159:15 |

| | | | |
|---|--|---|--|
| short-term 162:9 | simply 121:14 157:12 168:14 | 164:15,18 | 25:15 70:10 90:11 |
| shouldn't 54:17 | single 13:9 101:20 135:23 | smaller 19:10,11 88:1 | 120:10 143:22 147:12 148:22 |
| show 60:13,14 62:16 64:3 69:19 122:17 142:16 | sit 67:24 | smattering 9:24 | specified 67:15 |
| showed 55:3 58:17 60:23 64:7 117:3,6,10,18 | situation 114:12,18 122:3 | Smolin 103:24 | specifies 129:15 |
| showing 78:3 138:12 | situation-specific 120:22 | solid 138:9,15,21 139:8 140:16,20 142:13 143:3, 8,14 149:13,19 151:2,5 152:9 | speculate 143:22 |
| shown 49:1 64:1 68:5 69:5 75:10 123:14 126:20 127:22 155:5 | situations 94:16 | solubility 137:22 | speculated 128:24 130:1 131:21 141:18 |
| shows 53:9 65:12 78:3 107:20 155:5 | six 14:4,12 33:3,8,14 54:22, 25 56:21 57:23 64:1 65:14 66:21 72:6 119:22 | solution 53:18 137:23,24 139:5 | spent 14:19 |
| sicca 145:24 | six-month 64:5 | solutions 55:3 | spoken 13:20 |
| signature 14:7 | size 122:20 | somewhat 45:9 70:18 122:7 126:22 127:2 | sponsored 165:21 |
| significance 54:5 56:5,8,9 109:17 | Sjogren's 145:20 146:8 147:1 166:24 167:5 | Sonsini 15:8 | spot 54:2 |
| significant 55:4 56:17,18,19 57:6,24 58:1,2,9,18 59:18,19 61:7,9 62:12,17 64:4,8, 11 66:19 72:23 95:5,11 96:13 109:23 110:9 117:8,22 119:17,25 122:4 123:23 163:6,12, 14,24 164:3,11 | skill 52:21 59:1 60:3 61:15 70:6 156:16 157:14 161:11 | soon 80:14 | spots 53:24,25 |
| significantly 54:24 55:10,16 58:22,24 61:10 65:17 | skills 19:24 20:23 22:20 155:24 | soreness 76:22 | St 17:9 |
| similar 27:21 62:8 82:25 143:6 148:18 151:2 152:8 | skimmed 33:9,25 | sorry 15:7 39:24 40:1 47:13 54:13 67:4 73:7 105:7,14 146:15 151:14 155:12 157:7 169:1,17 | stage 26:24 28:6,12 77:18 |
| similarly 74:23 | skimming 67:19 | sort 26:18 31:5 75:5 78:15 88:17 89:11 90:2,11 91:5 110:14 122:9 138:20 145:7 | stages 27:5,6 |
| simple 90:16 | slight 141:4 | speaking 49:22 73:3 79:24 105:23 125:19 130:11,15 142:12 | staining 53:10,13,15 54:3 55:10 81:4,6 90:19 |
| simplest 121:13 | slightly 39:18 65:20 | species 146:6 | standard 56:6 72:12 73:9 93:8 109:9,16 110:2,14 |
| | small 53:20 60:6 65:19 73:1 78:3 87:24 92:14 96:5,8, 11 99:7 103:7,11,20 107:21 110:21 111:5 120:21 137:10 142:9 | specific 26:19 29:15 32:21 94:10 103:13 144:25 | standards 39:9 |
| | | specifically | standing 107:3 |
| | | | stands 11:24 46:17 133:14 136:24 |
| | | | start 7:25 33:2 115:13 146:16 153:12 |
| | | | started |

| | | | |
|---|--|--|---|
| 7:22 19:6 Starting 34:2 starts 21:24 59:24 128:12 144:5 state 7:9 55:2 89:1 114:8 128:13 132:11 147:23 stated 39:3 52:3 72:21 104:25 110:16 127:8 statement 18:17 45:12 72:19 73:4, 12 79:1 93:19 103:9 109:21 110:1 123:10 states 55:23 59:16,17 148:16 stating 70:22 113:18 statistical 20:2,10,11 56:8,9 73:14 109:17 164:1 statistically 54:23 55:4 57:6 58:2,18, 22 62:11,16 64:4,7,11 65:17 66:18 72:22 110:9, 13 117:7,22 119:17,25 123:23 163:14,24 164:2, 10 statisticians 123:13,17,19 statistics 19:21 20:4,6 stats 122:17 stature 95:20 step 8:3 steps 166:22 steroid 161:24 162:6,14 steroids 161:24 162:9 | Stevenson 90:18 91:22 stimulation 45:5 stimuli 44:1 stinging 76:20 83:20,23 104:16 stings 104:7 stop 55:21 167:15 strands 137:24 strange 59:2 60:16 91:5 stratified 126:8 streams 126:1 Street 7:14 stressed 54:8 stretch 78:17,19,21,22 79:18,19 strictly 94:12 105:23 130:10,15 142:11 strike 33:1 34:2 46:2 strip 53:19 strong 31:8 122:18 structures 129:13 STT 46:17 47:17 114:3 118:5 student 25:1 148:25 studied 59:12 studies | 21:7 27:7 30:5 51:11 62:25 67:3 77:17 87:8 118:13,23 156:11 158:21 164:24 study 30:22 31:15 50:16 53:9 59:11 73:21 77:14,20 80:24 102:12 107:13,20 117:18,23 118:2 119:8 120:9 121:3 122:13,14 127:23 142:14,15,22 143:25 144:2 147:22,24 150:25 152:17 156:13 161:5 subgroup 119:8,10 subgroups 121:20,21 subject 11:9 18:22 33:4 68:6,9 subjected 68:9 subjective 76:14,15,19 77:1 78:2 81:25 82:13 84:21 85:5 86:7,11,14 submission 133:6 submitted 124:18 133:4,8 165:22 subsequent 17:4 subset 145:21 substance 159:1 substantively 34:16 subtracting 45:17 success 87:20 suffering 31:4 sufficient 162:15 | sufficiently 95:2 suggest 71:3 74:20 150:20 Suggesting 151:3 suggests 68:18 74:5 149:19 155:9 suit 40:7 sum 89:6 summarize 29:7 summarized 148:19 superior 56:22,25 57:1 65:12,15 77:23 120:16,18 superiority 78:3 85:15 supplemented 131:11 supplied 99:9 supplies 149:22 support 165:22 supposed 69:2 supposedly 64:20 71:3 suppressed 29:19 66:22 119:5 sure 10:20 13:8 25:4 36:4 37:3 44:7 68:11 73:7,16 86:24 90:5 91:18,25 95:4,6 102:5 109:12 111:20 116:10 120:5 123:3 127:7 133:14 134:5 153:2 166:20 surface 27:9 30:14,18 31:16 81:11 83:2 85:19,22,25 |
|---|--|--|---|

| | | | |
|------------------------|--------------------------|---------------------------|--------------------------|
| 145:8 167:8 | 137:3 149:12 153:1 | 6,9,15,23 44:1,2 45:8,15, | tests |
| surfactant | 159:15 169:6 | 16,22,23 46:4 76:23,24, | 46:8 47:7,8 49:18 62:4 |
| 51:19 | taken | 25 79:6,14,22 80:1 167:9 | 63:4 68:1 121:16 |
| surfactants | 21:16 111:24 | technical | Teva |
| 51:22,25 | talk | 34:3 | 9:5 38:18 |
| surgery | 13:14,17 23:8 36:7,10,13 | technique | Texas |
| 23:19 | 79:10 134:9 143:9 | 126:11 | 9:12 |
| surgical | 145:13,18,22 148:9 | technology | text |
| 23:18 41:22 | 156:21 158:25 | 18:25 | 32:19 55:9 59:21 60:2 |
| surprised | talked | tell | 61:18 91:2 103:24 125:2 |
| 59:5,7 88:12 | 20:13 23:10 81:3,16,20 | 51:16,19 52:20,21 77:5 | Thank |
| switching | 85:16 87:18 118:8 | 100:1 160:19 | 17:10 35:19 89:5 132:14 |
| 11:13 | 124:15 127:6 137:9 | tells | 134:13 167:23 170:7,13 |
| sworn | 159:5 160:4 163:19 | 52:11 147:24 163:9 | Thanks |
| 7:4 | 166:21 | tend | 170:11 |
| syllabus | talker | 83:4 84:3 101:24 102:8 | theoretical |
| 33:20 | 8:2 | tended | 114:15 |
| symptom | talking | 149:25 | theoretically |
| 82:15 83:1,14 84:13 | 26:19,20 27:7 35:24 | tends | 114:11 |
| symptomatic | 38:19 52:18 73:24 90:11 | 82:15 152:12 | theory |
| 114:19 | 96:1 99:7 103:25 110:1 | term | 114:13 |
| symptoms | 129:8 131:19,20,24 | 11:12,13 40:24 65:16 | therapeutic |
| 41:6 42:5 47:18 76:15 | 141:22 151:7,8,9 | 130:19,24 138:12 | 41:8 125:7 126:1,8,20 |
| 84:1 86:3,16 | talks | 165:18,19 167:13 | 128:21 135:4 141:12 |
| syndrome | 141:25 146:1,25 147:2,3 | terms | 147:3 155:4,8 166:5,15 |
| 145:6,12,20 146:8,21 | target | 18:15 39:20 40:25 41:16 | 167:11 |
| 147:2 148:5 166:25 | 30:24 31:9 129:14 | 98:2 132:10 165:8 | therapeutically |
| 167:5 | targeted | 166:14 | 42:2,3 127:25 160:12 |
| system | 127:5,8 | test | therapies |
| 11:23 142:9 | tear | 44:12,16,23 45:7,13,19, | 126:19 |
| systemic | 29:13,17,18 30:1 42:7 | 20 46:17 53:19 59:7 | therapy |
| 131:11 142:8 | 44:12,15,17,19 46:17,20, | 62:19 75:16 99:1 104:11, | 126:10,15,16 134:22 |
| systemically | 24 47:1,17,21,22 48:3,8, | 21 108:6 111:8 113:19, | 135:2 141:10 |
| 145:18 155:7 | 13,15,19 49:1,3,17,21,22 | 24 121:17 144:9,14 | there's |
| | 54:20 64:2,9,21,22 66:21 | testified | 8:19 9:4 17:3 20:7 41:15 |
| | 67:9 78:9,13,16,24,25 | 7:5 | 44:25 50:15 52:10,20 |
| | 79:15,25 81:8,13,15,17, | testify | 57:5 62:7 66:8 68:18 |
| | 18,22 82:3,4,11,16,17,23 | 11:4 | 70:8 72:5 73:20 74:13,14 |
| | 83:5,6,12,18,19,24 84:4, | testifying | 77:1 91:16 92:5,11 96:25 |
| | 5,11,16 85:1,10,12,17,24 | 12:4 | 107:22,23 116:3 119:13, |
| | 86:4,6,13,19,21 108:6 | testimony | 24 123:3 130:7 135:14 |
| | 113:19 116:16,25 117:3 | 12:6,11 149:12 159:1,24 | 137:18,25 138:6 139:1, |
| | 119:4 153:17,21,24 | 164:22 | 12,14 144:4 152:3 155:9 |
| | 154:4,15,21 160:13 | testing | 165:7 166:13 |
| | 163:1,7,10 | 103:23 104:1 110:11 | thereof |
| | tearing | 114:17 121:15 | 37:16 |
| | 74:6,21 75:10,20,21 | thermodynamic | |
| | 104:6,10,15 114:16 | | |
| | tears | | |
| | 42:11,12,16,19,25 43:2, | | |
| | | | |
| table | | | |
| 96:24 97:5 108:5 126:5 | | | |
| 135:20,24 136:1,9 | | | |
| 137:15 138:13 139:7 | | | |
| 151:21 155:5 | | | |
| take | | | |
| 8:16,21 16:12 44:5 | | | |
| 80:13,15 86:22 108:25 | | | |
| 110:15 111:23 120:23 | | | |
| T | | | |

| | | | |
|--|---|---|--|
| 156:19 157:14 158:3,13 thermodynamics 157:21 they're 26:1 42:20 43:3,17 47:7 66:15 75:1 76:13 86:16 91:7 99:4 119:11 124:13 126:24 127:4 140:3 141:9 151:6,8,9,11,23 158:16 159:11 they've 126:14 thing 8:14 13:9 43:22 47:4 65:9 66:3,5 75:6 88:6 90:7 94:21 122:14 148:22 150:15 155:1 166:16,21 things 9:24 75:23,24 78:11 79:20 90:15,16 109:25 121:2 137:14 146:9,24 162:18 think 10:1,19 11:2,10 12:24 15:11 16:7 19:7 20:7,8 21:21 27:12 29:7 32:11, 23 37:1 38:1 39:2 41:14 42:14 43:14 45:11 47:6 48:5 49:16 52:18,20 54:25 56:2 57:14 58:5,12 60:20 61:13,14,25 65:3 66:6,8 67:16 68:22 69:8 70:15 73:6 74:13 75:1,4, 12 78:17,19,22 80:8,11, 19 81:3 82:1,25 89:6 91:8 92:6 93:16,20,24 95:13,18 101:15 103:9 104:3 106:7 107:2 109:15 110:6 111:14 114:20 116:9 117:4 121:12 123:10 124:10, 13,15 125:5 132:10,11 134:18 136:3 137:18 138:10,11 139:9 143:4, 10 146:3 147:5 149:10, 14,15 151:14 154:6 155:1 158:21 160:21 161:18 166:12,13,16,21, 23 168:11 thinking 59:2 70:16 116:6 | thought 18:23 19:4 23:3 35:23 46:19,25 92:3,5 94:2 100:9 122:7 169:17,19 thousand 147:9 three 44:25 45:2 57:10 63:10 74:16,18,25 96:12 three- 64:6 three-month 74:15 threshold 121:14 125:6 thoroughly 119:14 thrust 30:13 32:23 time 10:23 14:19 24:4,11,21, 25 25:8 30:21 43:21 53:16 55:2 56:19 57:8, 19,20,22,23 58:18,19,23 59:8,10 60:24 62:22 64:5,7,13,21 65:21 69:14 70:7,12 74:20 77:24 78:5 88:12 90:10,16 93:13 108:23 109:3 110:10 119:3 136:14 159:14 163:15 164:4 times 7:19 8:23 39:3 99:13 tissue 53:22 129:14 132:3,7 136:19,20 137:25 138:15 139:25 140:16,18,22 141:1 142:13,20 143:3,6, 8,13 144:17,25 145:2 146:4,20 147:2,14 149:4, 9,13,19 150:1,5,17,20,23 151:6,16 152:12,14,18, 24 154:4 155:5,10 160:6 tissues 131:25 145:6,11,15 146:5 147:14,25 148:4, 14,18 149:1,16,21 151:2 152:3,9,25 154:15,21 161:8 | titled 126:7 today 12:4,6,11,14 15:20 67:24 92:2 156:10 158:25 159:2 told 96:9 tonight 170:10 top 10:3 32:5,15 35:10 40:18 49:15 107:25 128:8,19 141:17 topic 69:21 topical 41:21 45:3 67:10 125:23 131:10 134:22 135:2 141:9 142:3,7 143:24 144:5,7,17 147:16 156:2, 4 topically 137:11 146:1 total 45:25 47:21 64:9,21 89:6 totality 116:6,11 120:9 152:23 153:8 Totally 98:17 toxicity 27:8 tract 130:12,22 Trademark 11:25 12:2 training 19:24 20:24 22:20 34:13 155:24 transcorneal 142:5 transcript 8:11 54:14 69:1 152:7 168:10,19 169:15 170:3, 4 | transcripts 168:15,21 translate 98:24 107:14 transplant 125:22 150:2 161:8 transplantation 125:18 128:22 151:24 160:6,8 transplantations 160:1 transplanted 126:9 transplants 25:5 transport 149:25 150:9,22 Travatan 27:7 28:8 travoprost 27:7 30:20 treat 30:17 91:6 143:23 145:6 161:22,23 167:4,5,6,7 treated 58:10 88:1 125:22 treating 31:11,17 treatment 28:13 29:2,4,11,24 30:14 31:2 41:18 50:10 59:20 61:9 72:7,11,13 74:5 75:20 84:22 85:8 109:8, 10 122:16 131:9 145:12 146:20 148:5,15,17 166:17 167:1,14,16 treatments 30:10 40:13,25 41:13,22, 23 72:10 121:20 166:6,9 trend 55:15 trial 10:20 trials 21:2 22:24 25:24,25 26:8,10,14 27:10,14 30:3 |
|--|---|---|--|

| | | | |
|--|--|--|---|
| 50:9 61:25 123:14 165:5, 14,15,16,20,21 | 80:1 129:11,14 130:17, 18,24 131:9,12 138:19 140:16 161:24 165:4,21 | 149:1 165:20 167:13 | uvea 130:11 |
| tried 39:13 65:4 | typo 136:9 138:24 | understanding 11:18,20 14:13 21:6 49:9 53:2 61:24 69:4,21 70:20 93:6 95:16 116:19 123:21 124:6 125:24 147:16 155:25 | uveal 130:12,22 |
| triple 126:15,16 | typos 138:1,10 | understood 35:19 102:6 166:1 | uveitis 128:15,24 129:10 130:1, 8,11,15,19,25 136:25 141:18 143:18,20,24 148:7 161:1,14 162:5 |
| troubled 60:4 | <hr/> U <hr/> | unexpected 69:4,19 70:23 71:6 115:22 | <hr/> V <hr/> |
| true 30:5,7 45:6 63:20 79:1 87:6 121:2 125:20 141:22 156:7 | U-v-e-a 130:12 | unfortunately 101:12,13 102:25 167:2 | vague 94:11,14 |
| truthful 12:11 | U-v-e-a-l 130:12 | unhealthy 54:7,15 | validity 11:22 122:11 |
| try 8:2,3,16 100:11 106:6 143:9 151:18 | U.S. 12:1 33:21 | unique 149:9 | value 55:23,25 57:11 60:5 62:3 63:9,19,24 64:4 68:19 72:8 73:25 97:1 163:23 |
| trying 8:11 38:4 41:25 91:9 98:22 102:6 103:5,8 105:18 114:11 119:1 146:23 162:17 | UCSF 24:19 | unit 60:13 | values 57:16 68:2 89:13 93:25 98:12,13 101:21 107:23 110:16 111:13 127:22 |
| turn 14:6 31:18,19 39:22 47:10 72:2 113:4 121:2 124:21 125:10 134:20 | Uh-huh 73:22 89:10 96:21 97:21 | units 72:25 78:4 90:17 91:4 98:23 164:17 | variability 103:22,25 104:2 |
| twice 162:13 | uh-huhs 8:13 | unpredictable 60:8 | variable 104:12 164:11 |
| two 8:25 9:6 17:6 18:3,4 39:10,19 42:10 45:25 50:8,9 57:2,20 64:17 93:17,25 95:2,5,11 96:12 121:20 142:21 162:7 165:4 | ultimately 87:21 89:24 97:19 | unusual 114:20 | variables 59:12 63:2 |
| type 82:3,16 83:4,16 84:4,13 85:11 86:18 93:18 150:19,23 | unable 164:6 | update 17:10 | variety 62:4 81:1 86:2 88:6 121:12 148:18 149:1,16 152:3,9,25 153:10 161:7 |
| types 29:3 42:11 43:4 54:10,11 62:13 83:15 84:14 110:11 149:3,4 151:25 161:22 162:12 | uncommon 91:6 | urgency 131:13 | various 12:15 13:10,11,13 18:7,8 20:25 21:3,4 32:7 35:2 40:13 41:16 42:20 54:9 84:1 154:8 156:3,11 162:20 |
| typical 146:6 | underlies 94:22 115:21 116:11 | use 17:19 28:21,24 29:8 39:15 42:15 60:4 62:2,3 76:23,25 79:6,14,21 80:1 85:17 91:14 107:15 125:17 130:19,24 162:4, 9 165:2 | vary 43:21 104:18 |
| typically 29:8 43:8,9 53:15,22 | underlined 97:16 | useful 103:10 121:7 147:16 | vehicle 50:20,23 51:8,11,17,20, 23 52:1 54:24 55:3,11,17 56:23 57:12 58:3,10,17 59:19 60:25 61:8,11 63:10 64:1,3,7,20 65:13 |
| | underlining 97:17 | uses 66:10 | |
| | underlying 31:10 53:22 59:3 107:13 116:22 | usual 138:15 | |
| | understand 8:7 11:15,19 12:3 14:11 18:18 20:1,10,13 23:21 29:12 31:1 47:6 48:1 50:3,6 59:14 60:19 74:12 81:24 86:1 91:4,10 93:3 99:13,17 102:5 104:23 107:16 114:3 119:14 120:5 123:7,12,16 125:21 129:9 135:9 | usually 129:13 131:5 | |

| | | | |
|--|--|--|---|
| 66:20 67:4 87:20 88:1 119:22,23 123:25 163:14 | Wait 134:23 | weight 117:25 120:14,18,21 139:19 | 8:19 63:17 |
| vehicle-treated 67:8 124:2 | want 46:12 47:11 59:5 68:4, 13,20 87:14 108:19,25 113:12 121:1 124:21 151:10 152:6 | well-controlled 117:18 165:5 | word 160:16 164:23 165:2,13 |
| venues 39:11 | | Wendy 12:25 15:10 | worded 119:3 |
| verbally 8:12 | wanted 91:1 | went 10:19 18:1,3 74:21 100:13 140:6 151:15 160:21 | words 52:15 93:5 99:3 115:4 155:21 |
| verge 70:19 | wasn't 100:7 109:12 147:11 148:8 151:15 | weren't 35:5 | work 15:18 19:10 21:10 22:18 75:10 125:14 |
| verify 108:17 164:2 | watch 8:3 | wetting 66:19 87:7 101:8 113:9 119:18 120:1 123:24 | worked 123:18 136:19 |
| verse 91:19 | water 52:5 138:17 139:22,23 141:2 158:5 | what's 7:12 11:23 13:24 16:14 24:17 42:1,3 49:5,23 51:9 60:18 64:25 71:22, 24 77:5 167:10 | working 14:14 20:25 21:2 24:2,9 |
| version 37:16 49:11 | way 27:25 31:7 39:18 40:8 45:14 54:3 56:3 60:16 75:14,15 91:5,6 101:13 102:16 119:3 123:5 137:19,25 138:6,15 139:1 140:22,23 163:19 165:11 | Where's 110:1 | works 115:10,15,16 116:7,8 |
| versions 17:5 | ways 44:25 45:2 | white 52:15 131:6 154:10,18, 24 | world 95:15 150:15 |
| versus 39:15 66:20 67:7 92:17 119:22,23 123:25 124:2 | we'll 8:2,16,19 20:12 | wide 62:4 148:18 149:1,5 | worse 72:8 104:2 |
| view 39:4 113:18 118:8 146:7 | we're 38:19 52:18 85:3 96:1,4 99:6 105:20 122:14,15 129:1 134:9 137:4 152:21 156:21 162:6 | Wilson 15:6,8 | worsening 58:9 59:18 61:8 |
| vision 76:4,7,21 78:8,10,12,23 79:21 81:20 | we've 68:15 81:3,16,20 85:16 88:17 113:7,8 118:8 127:6 136:21 138:2 141:20 143:16 151:20 | Winschel 15:9 | wouldn't 31:6 92:24 96:9,13 99:8 137:21 |
| vision-threatening 161:16 | WEDNESDAY 7:1 | withdraw 166:19 | write 109:19,20 |
| visits 55:5 | week 76:25 | witness 15:24 19:1,10 20:15 35:14,23 37:9,16 44:7 48:5 50:23 51:14 52:7,14 56:25 57:14 58:12 65:3 68:4 69:8 75:23 78:1 79:9 87:11 88:23 98:17 99:17 100:6 102:15 103:5 106:3 108:23 109:2 115:25 118:25 120:5 124:4 134:12,13 143:12 146:23 147:22 155:17 156:21 157:17 | written 16:8,9 |
| visual 77:11 | weigh 140:10,22 141:1 | won't | wrong 72:19 95:18 115:12,13 125:5 137:18 |
| vitreous 136:19 137:23 138:19,22 139:3,14,15 140:10,20 143:12 152:19 161:3 | weighs 138:17 139:23,25 140:11 | | wrongful 10:5 |
| volume 139:16 140:23 | | | wrote 116:18 |
| <hr/> W <hr/> | | | WSGR 15:3 99:18 |
| W-e-t-t-i-n-g 66:20 | | | <hr/> Y <hr/> |
| W-i-n-s-c-h-e-l 15:10 | | | yeah 11:6 22:1 43:11 47:6 63:21 80:7 94:22 97:11 102:15 107:19 111:23 |

116:20 128:5,6,11 135:1,
17 137:18 146:23 157:11
169:21

year

10:25 33:15

years

17:21 18:4,22 19:3,25
20:24 22:17,18 23:4,8,12
31:15 34:12 90:9 155:22,
23

Yeses

8:12

Yesterday

12:19

you'd

51:10 72:2 89:2 111:16
125:16 140:16,19 154:12
155:18

you're

7:23 12:3 18:18 21:13
27:6 38:24 45:24 53:16,
17 58:12 60:11 62:9 63:1
87:11 88:23 90:12 95:5,
17 97:25 101:20,22
106:25 109:24 110:1,6
113:18 121:15 122:9
124:8 130:3 132:11
133:19,21 138:7 139:9
140:8,9 146:13,23

you've

7:16 8:23 9:20 17:23
23:22 30:3 39:3,13 40:6
44:14 53:1,4 71:11,17
90:6 93:10 98:12 99:12
103:2 104:13,15 124:18
125:1 132:1 152:1 159:4

young

139:17

Z

zero

76:14 77:7 78:4 90:18,19

Zymaxid

10:22