

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

3 -----
4 MYLAN PHARMACEUTICALS INC.,
5 Petitioner

6 vs

7 NOVO NORDISK A/S,
8 Patent Owner
9 -----

10 Case IPR2023-00724

11 U.S. Patent No. 10,335,462
12

13 Oral deposition of
14 ALLEN SPIEGEL, M.D.
15

16 VIA VIDEO/TELECONFERENCE

17 FRIDAY, JULY 26, 2024

18 10:03 a.m. EASTERN TIME
19

20 Job No.: 534601

21 Pages: 1 - 154

22 Reported by: Lisa V. Feissner, RDR, CRR, CLR

1
2
3 Oral deposition of ALLEN SPIEGEL, M.D.,
4 held REMOTELY, via ZOOM, on FRIDAY, JULY 26, 2024,
5 BEGINNING at 10:03 a.m., pursuant to NOTICE, before
6 Lisa V. Feissner, RDR, CRR, CLR, Notary Public.
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22

Transcript of Allen Spiegel, M.D.
Conducted on July 26, 2024

3

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22
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C O N T E N T S

EXAMINATION OF ALLEN SPIEGEL, M.D.	PAGE
By Mr. Reich	5

P R E V I O U S L Y

M A R K E D E X H I B I T S

(identified but not attached)

EXHIBITS	PAGE
MPI Exhibit 1117	112
MPI Exhibit 1302	12

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P R O C E E D I N G S

ALLEN SPIEGEL, M.D.,

having been first duly sworn, was examined and
testified as follows:

EXAMINATION

BY MR. REICH:

Q Good morning, Dr. Spiegel.

A Good morning, Mr. Reich.

Q Have you ever been deposed before?

A No.

Q Okay. So I'm sure counsel went over some
of the basics, but just to cover a few ground rules
so we have a smooth recording and transcript.

First, everything is being transcribed,
so it's very important that we don't talk over each
other. I'll do my best to ask a question, let you
respond. And I'm sure if your counsel has any
objections, it would be good to pause so we just
have a clean transcript. I think Lisa would
appreciate that.

Is that fair?

A It is fair.

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1 And I want to just quickly qualify my
2 "no" answer. I answered "no" with regard to any
3 patent issues. I was deposed as the dean of the
4 Albert Einstein College of Medicine in a suit
5 brought by a student who had been expelled before my
6 time. So that's the only time I've been deposed,
7 not pertinent to this type of proceeding.

8 Q And when was that deposition?

9 A 2006.

10 Q Okay. So it's been a bit. So I'll still
11 cover the ground rules. But I appreciate you
12 clarifying.

13 Second, please provide verbal answers.
14 Head shakes won't be caught on the transcript. So,
15 you know, it's very natural to want to shake your
16 head, but please do your best to give a verbal
17 answer.

18 Fair?

19 A Yes.

20 Q And then I'm going to do my best to ask
21 clear questions that hopefully you understand. But
22 if you do not understand the question, please let me

1	know. I'll try to restate it. But if you don't ask	10:05:21
2	for a restatement, I'm going to assume you	10:05:24
3	understood what I asked.	10:05:26
4	Is that fair?	10:05:27
5	A That is fair.	10:05:28
6	Q I'll also try to take regular breaks.	10:05:29
7	But if you need to take a break, let us know, we'll	10:05:31
8	try to accommodate it. But if a question is	10:05:34
9	pending, I'll just ask that we finish the question	10:05:35
10	and then we break.	10:05:38
11	Fair?	10:05:39
12	A Thank you.	10:05:39
13	Q What did you do to prepare for today's	10:05:40
14	deposition?	10:05:42
15	MR. ANSTAETT: And Doctor, I'll just	10:05:45
16	caution you that you can tell Mr. Reich who you met	10:05:46
17	with, when you met with, what you reviewed, but	10:05:50
18	don't reveal the content of any conversations you	10:05:52
19	had with lawyers.	10:05:54
20	THE WITNESS: Understood.	10:05:55
21	A What I did to prepare is to read and	10:05:56
22	re-read the copy of my reply to Dr. Goland's	10:05:59

1 declaration, read her declaration, read the 10:06:06
 2 deposition that she gave with Mr. Anstaett. And 10:06:10
 3 then I had communication with the attorneys and some 10:06:15
 4 prep for just the format of a deposition. That was 10:06:23
 5 my preparation. 10:06:27

6 Q Okay. Other than the attorneys, did you 10:06:28
 7 meet with anyone else to prepare for today's 10:06:30
 8 deposition? 10:06:33

9 A No. 10:06:35

10 Q Did you discuss today's deposition with 10:06:37
 11 anyone other than the attorneys? 10:06:39

12 A I may have mentioned something to my 10:06:43
 13 wife. She's aware of the fact that my absence is 10:06:45
 14 due to being here. 10:06:47

15 Other than that, no. 10:06:49

16 Q That's fair. Probably good to notify her 10:06:51
 17 where you are today. 10:06:55

18 How long did you meet with the attorneys 10:06:57
 19 from Perkins? 10:06:58

20 A I would say the average total would be 10:07:01
 21 about six hours. 10:07:05

22 Q To be clear, did you meet with any 10:07:08

Transcript of Allen Spiegel, M.D.
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1	attorneys other than attorneys from Perkins?	10:07:10
2	A No, not to my knowledge.	10:07:13
3	Q And what do you have with you in the room	10:07:18
4	today?	10:07:21
5	A What I have in the room, there's a large	10:07:22
6	cardboard box with printouts of all the items listed	10:07:27
7	in the appendix as well as the list of abbreviations	10:07:34
8	and just a pad to jot some notes on.	10:07:39
9	Q There's no notes on that pad right now?	10:07:42
10	A I have some notes on the pad. I have a	10:07:47
11	quick summary of my understanding of some of the	10:07:51
12	relevant patents, some of the relevant doses, just a	10:07:55
13	mnemonic device. But it's very limited material.	10:08:01
14	MR. ANSTAETT: And I'll say, Josh, I	10:08:06
15	didn't realize that he had that with him. We can	10:08:08
16	certainly take that away.	10:08:10
17	THE WITNESS: No problem. I'll tear it	10:08:13
18	up right now.	10:08:15
19	It's gone.	10:08:18
20	Q Do you have notes on any of the paper	10:08:21
21	copies that you have other than the notepad?	10:08:24
22	A I have notes on previous copies that I	10:08:26

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1	used to review. But these are all clean copies.	10:08:29
2	Q And do you have anything up on the screen	10:08:34
3	right now other than this Zoom?	10:08:44
4	A Four quadrants with the folks that are	10:08:49
5	relevant in it. That's it.	10:08:52
6	Q Okay. And if anything comes up on the	10:08:54
7	screen, will you let me know?	10:08:57
8	A Of course.	10:08:59
9	Q I'm otherwise going to assume that the	10:09:01
10	only thing you have in front of you are the clean	10:09:04
11	paper copies and the Zoom window.	10:09:06
12	Is that fair?	10:09:09
13	A Zoom window, yes. The clean copies are a	10:09:11
14	little bit distant, but I may call to see those in	10:09:13
15	response to your questions, just to let you know.	10:09:18
16	And I have a blank pad where I may just	10:09:22
17	scribble notes on your question.	10:09:25
18	Q Okay. And did you look at anything other	10:09:27
19	than Dr. Goland's deposition transcript that is not	10:09:32
20	identified in your list of materials considered to	10:09:35
21	prepare for today's deposition?	10:09:39
22	A Could you restate that? I'm not sure	10:09:42

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1	what you mean by other than her deposition.	10:09:44
2	Q Did you look at anything to prepare for	10:09:46
3	today's deposition that is not identified in your	10:09:55
4	list of materials considered in the back of your	10:09:58
5	declaration?	10:10:01
6	A Ah, list of materials considered.	10:10:04
7	No, I did not.	10:10:06
8	Q And did you look at Dr. Goland's	10:10:16
9	declaration before or after you wrote your	10:10:19
10	declaration?	10:10:20
11	A Before.	10:10:22
12	Q All right. So you understand you're here	10:10:27
13	today because you've provided a declaration in	10:10:29
14	IPR 2023-00724?	10:10:31
15	A I can't attest to the fact that I know	10:10:36
16	that particular number, but I do recognize the term	10:10:39
17	IPR. So presumptively, yes, assuming that number is	10:10:43
18	the one relevant to this IPR.	10:10:48
19	MR. REICH: And if we could pull up	10:10:52
20	Exhibit 1302. And Dave, if you want to hand him his	10:10:54
21	paper copy, that's fine with me, too.	10:10:57
22	MR. ANSTAETT: Okay. We'll get it for	10:10:59

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1	him.	10:11:00
2	(Previously marked Exhibit 1302 presented	10:11:00
3	to the witness.)	10:11:03
4	MR. ANSTAETT: He's got it now.	10:11:03
5	THE WITNESS: Yes, I now have it, and I	10:11:05
6	do see 2023-00724 with a footnote also to	10:11:07
7	IPR 2024-0009.	10:11:15
8	BY MR. REICH:	10:11:18
9	Q And do you see in the bottom right	10:11:18
10	corner, it's marked as Exhibit 1302?	10:11:20
11	A I do.	10:11:24
12	Q So today if I refer to this as your	10:11:26
13	declaration or Exhibit 1302, do you understand that	10:11:28
14	what I am referring to is your reply declaration?	10:11:31
15	A I do.	10:11:35
16	Q Does this declaration reflect the	10:11:37
17	complete opinions that you've offered in this	10:11:42
18	proceeding?	10:11:45
19	A Yes, they do.	10:11:47
20	Q And when you reviewed your declaration,	10:11:48
21	did you have any corrections you wanted to make?	10:11:51
22	A No.	10:11:55

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1	Q	Are you familiar with Dr. Goland?	10:12:01
2	A	Yes, I am.	10:12:04
3	Q	Can you explain how you're familiar with	10:12:09
4		Dr. Goland?	10:12:11
5	A	Of course. As listed in my reply	10:12:12
6		declaration, and I can point to the specifics pages	10:12:17
7		if you wish, where it lists my qualifications and	10:12:19
8		experience, you may see that I was the director of	10:12:23
9		the National Institute of Diabetes and Digestive and	10:12:25
10		Kidney Disease at the National Institutes of Health,	10:12:29
11		NIH henceforth, and that was from late 1999 until	10:12:32
12		the spring of 2006.	10:12:36
13		During that period of time, perhaps 2004,	10:12:37
14		and I cannot attest to the accuracy of that specific	10:12:41
15		year, as part of my responsibilities as the director	10:12:44
16		of NIDDK, the diabetes institute, I would visit	10:12:48
17		various of our funded diabetes centers, one of which	10:12:52
18		was at Columbia medical school.	10:12:56
19		Dr. Goland was one of the co-directors of	10:13:01
20		the Berrie Diabetes Center at Columbia. I gave a	10:13:05
21		grand rounds at Columbia on that visit, and I	10:13:11
22		visited with her in the physical facility of the	10:13:14

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1 Berrie Center.

10:13:16

2 That's the one time that I encountered
3 her. And I believe that the group at Columbia also
4 took me out to dinner at a New York restaurant, for
5 which I did not allow them to pay because, as a
6 government employee, I was a stickler for following
7 those rules.

10:13:20

10:13:22

10:13:25

10:13:28

10:13:33

10:13:36

8 So I did meet Dr. Goland in that context,
9 but that was the only direct contact I had with her.

10:13:37

10:13:39

10 Q Is the Berrie Diabetes Center a
11 well-known diabetes center, in your opinion?

10:13:45

10:13:48

12 A Can you define what you mean by
13 "well-known"?

10:13:51

10:13:54

14 Q Is it a prestigious diabetes center?

10:13:56

15 A Its prestige is largely local. What I
16 mean by that is that it's known in the New York City
17 metropolitan area as a good diabetes center.

10:14:02

10:14:07

10:14:11

18 But I have to dichotomize here. I said
19 that Goland was the co-director, and that's because
20 there are two other individuals whom I know
21 substantially better than Dr. Goland, and that's
22 Dr. Rudolph Leibel, L-E-I-B-E-L, and Dr. Domenico

10:14:15

10:14:18

10:14:23

10:14:25

10:14:28

1	Achilli. I won't try to spell that name.	10:14:36
2	They are co-directors of the Berrie	10:14:39
3	Center. They are noted physician scientists, and	10:14:41
4	their important research accomplishments in diabetes	10:14:44
5	research lends prestige to the Berrie Diabetes	10:14:46
6	Center.	10:14:51
7	Q Are you aware of who founded the Berrie	10:14:51
8	Diabetes Center?	10:14:56
9	A I believe, in reading her declaration,	10:14:56
10	she takes credit for -- that -- she, that being	10:14:58
11	Dr. Goland, takes credit for founding it. So I am	10:15:02
12	aware of that.	10:15:07
13	I don't have any verification of that or	10:15:08
14	independent knowledge that that is true. But she	10:15:11
15	made that statement, and I have no reason to doubt	10:15:13
16	her.	10:15:15
17	Q So you referenced your role at the NIH.	10:15:21
18	Is that correct?	10:15:24
19	A That is in my reply, yes.	10:15:24
20	Q And you said that you were the scientific	10:15:27
21	director of the division of -- I'm sorry. Strike	10:15:33
22	that.	10:15:38

1 Could you tell me what NIDDK stands for 10:15:38
2 again. 10:15:43

3 A Absolutely. And I should preface that by 10:15:43
4 saying that the names of the various institutes and 10:15:47
5 centers at the NIH, of which there are approximately 10:15:50
6 26, are a function of various lobbying groups, 10:15:54
7 disease advocacy groups. 10:15:58

8 So the name of institute which I headed 10:16:00
9 has changed over the years. But the name when I was 10:16:02
10 the director was the National Institute of Diabetes 10:16:04
11 and Digestive and Kidney Diseases, NIDDK. 10:16:07

12 Q And you wrote in your reply declaration 10:16:13
13 that you were responsible for the oversight of major 10:16:16
14 national clinical trials in diabetes. 10:16:18

15 Does that ring a bell? 10:16:20

16 A Yes, it does. 10:16:24

17 Q What were those major national clinical 10:16:26
18 trials that you oversaw? 10:16:29

19 A They were under the auspices of each of 10:16:35
20 the divisions that I've described, so there are 10:16:37
21 separate divisions within the institute I headed for 10:16:39
22 diabetes, for digestive disease, for kidney disease. 10:16:42

1	I assume, unless you are interested, I	10:16:46
2	won't go into the digestive disease national	10:16:48
3	clinical trials. I won't go into the kidney disease	10:16:52
4	clinical trials. But I'll confine myself to the	10:16:55
5	diabetes trials.	10:16:57
6	Is that appropriate?	10:16:58
7	Q Yeah. We can start with the diabetes	10:17:00
8	trials.	10:17:02
9	A And then I'll dichotomize those, because	10:17:03
10	within the diabetes trials, there are some focused	10:17:06
11	on type 1 diabetes and others focused on type 2	10:17:10
12	diabetes.	10:17:15
13	Shall I confine myself to the type 2	10:17:16
14	diabetes?	10:17:18
15	Q Yeah, that sounds fair.	10:17:19
16	A Good.	10:17:20
17	So one of the major trials current during	10:17:26
18	my time as director spanned -- and I want to just	10:17:28
19	clarify, this is as the institute director. The	10:17:31
20	terminology which you started into can be a little	10:17:34
21	confusing.	10:17:36
22	From '90 to '99, I was the scientific	10:17:37

1 director, is the terminology, the director of the 10:17:40
2 division of intramural research. From late 99 until 10:17:43
3 spring of 2006, I was the director, the institute 10:17:47
4 director of NIDDK. 10:17:51

5 During that period of time, major trials 10:17:52
6 that we had, one was called DPP, the Diabetes 10:17:54
7 Prevention Program. And strictly speaking, that 10:17:58
8 trial addressed approximately 3400 individuals, not 10:18:01
9 with diabetes, but with what later became to be 10:18:05
10 termed as a result of this trial outcome 10:18:09
11 prediabetes. 10:18:12

12 And in these individual, the question 10:18:13
13 was, can you prevent the subsequent development of 10:18:16
14 overt diabetes in these individuals. 10:18:20

15 And the answer turned out to be, yes. 10:18:23
16 That trial was ended early because the Data Safety 10:18:26
17 and Monitoring Board -- and I should stress that I 10:18:31
18 attended religiously the national investigator 10:18:32
19 clinical trial meetings as well got reports from 10:18:38
20 Data Safety and Monitoring Board. 10:18:41

21 There were three arms while I was the 10:18:43
22 director, and one arm was a control, which was 10:18:45

1	conventional lifestyle information.	10:18:49
2	The second arm was an intensive lifestyle	10:18:52
3	intervention to achieve some degree of weight loss	10:18:55
4	and more healthy diet and exercise.	10:18:59
5	And the third arm was metformin.	10:19:02
6	And the results were reported in New	10:19:05
7	England Journal, and it turned out that you had a	10:19:10
8	58 percent reduction in subsequent years of	10:19:13
9	follow-up with the intensive lifestyle intervention;	10:19:16
10	a somewhat lower degree of prevention, in the	10:19:21
11	35 percent range, for metformin, all by comparison	10:19:25
12	to placebo.	10:19:28
13	So that was a major trial conducted	10:19:30
14	during that period of time in the type 2 diabetes	10:19:31
15	relevant space.	10:19:34
16	Shall I go on?	10:19:36
17	Q We can pause on this one.	10:19:37
18	So you said that that trial ended early.	10:19:46
19	Is that correct?	10:19:48
20	A It ended -- and I'm mindful, as I sit	10:19:48
21	here looking out the window in New York City, it	10:19:52
22	ended just pre-9/11.	10:19:55

1 In August of 2001, I and a man named 10:19:57
2 David Nathan, the overall head, from an academic 10:20:03
3 center point of view, of the trial, the lead 10:20:11
4 investigator, as it's called, both came to New York 10:20:14
5 as part of press conferences and interviews that we 10:20:17
6 had to report the results of that trial. 10:20:22

7 So August 2001. 10:20:24

8 Q And when you had testified it ended 10:20:30
9 early, that was because it had a predetermined end 10:20:32
10 point? Or sorry. Can you explain that a little bit 10:20:37
11 more? 10:20:39

12 A Of course. As you may know, when 10:20:40
13 clinical trials, multicenter trials of this 10:20:43
14 magnitude are conducted, it's standard procedure to 10:20:45
15 have an independent Data Safety and Monitoring 10:20:49
16 Board. 10:20:52

17 And they meet periodically, and they 10:20:52
18 don't have the authority themselves to stop the 10:20:56
19 trial, but they report to me, as the institute 10:20:59
20 director, and to colleagues who work under me at the 10:21:03
21 institute to recommend a course of action. 10:21:06

22 And there can be two reasons for early 10:21:11

1 cessation of the trial.

10:21:14

2 One, the very fortunate one, positive one
3 in this case, that the results are so clearly
4 beneficial that one can question what's called
5 equipoise, the ethics of continuing to give a
6 placebo and not the active, in this case, intensive
7 lifestyle intervention.

10:21:15

10:21:18

10:21:20

10:21:27

10:21:31

10:21:36

8 Of course, the other reason can be
9 futility, and that's a term of art in the clinical
10 investigation space which means it's very clear that
11 you're never going to achieve the prespecified
12 objectives, and so it's unfair and possibly
13 inappropriate to continue subjecting the patients
14 enrolled in the trial.

10:21:38

10:21:40

10:21:43

10:21:45

10:21:48

10:21:52

10:21:56

15 So does that answer your question?

10:21:57

16 Q Yeah. How common is it that a trial ends
17 early because it's unethical to proceed with giving
18 patients a placebo?

10:21:59

10:22:03

10:22:07

19 MR. ANSTAETT: Objection to form.

10:22:09

20 A I cannot specify in the universe of
21 clinical trials that percentage. It's relatively
22 rare, but it does occur.

10:22:13

10:22:17

10:22:19

1	Q	And is it a notable outcome when it	10:22:21
2		occurs?	10:22:25
3		MR. ANSTAETT: Objection to form.	10:22:25
4	A	I'm not sure what you mean by "notable."	10:22:27
5	Q	You said you flew up to give a press	10:22:31
6		release.	10:22:32
7		Is that correct?	10:22:33
8	A	I want to explain that type 2 diabetes	10:22:34
9		and prediabetes -- by the way, that terminology was	10:22:42
10		adapted by the American Diabetes Association	10:22:45
11		subsequent to this trial because it became clear	10:22:48
12		that there is value to identifying such individuals	10:22:51
13		because you have means of preventing their	10:22:54
14		development of diabetes.	10:22:57
15		In the aggregate, this affects some	10:22:58
16		98 million people in the United States. That's of	10:23:02
17		great interest from a socioeconomic point of view,	10:23:04
18		from a health point of view.	10:23:08
19		So yes, there was press interest, and	10:23:09
20		that is the reason for the interviews by media.	10:23:12
21	Q	And for the, you said, aggressive	10:23:15
22		lifestyle intervention arm -- is that the proper	10:23:24

1	term?	10:23:27
2	A Intensive lifestyle intervention.	10:23:28
3	"Aggressive" has a little bit of a negative	10:23:33
4	connotation.	10:23:35
5	Q What did the intensive lifestyle	10:23:36
6	intervention arm entail for treatment?	10:23:39
7	A What it entailed -- and I'm stressing,	10:23:43
8	there was no pharmacologic treatment of these	10:23:47
9	individuals. It involved sessions with appropriate	10:23:50
10	counselors, dieticians that focused on healthy diet,	10:23:55
11	the macronutrient composition of the diet, that is,	10:24:02
12	how much fat, how much carbohydrate, how much	10:24:07
13	protein, the frequency of eating the meals, and then	10:24:11
14	very importantly, also the exercise.	10:24:16
15	And what I want to stress -- and this is	10:24:20
16	very much part -- I want to just perhaps anticipate	10:24:24
17	part of what you're saying -- the successful outcome	10:24:28
18	of the trial led to a major educational program	10:24:32
19	around the country to inform the public,	10:24:36
20	particularly those individuals at great risk of	10:24:40
21	developing diabetes -- and the risk factors are	10:24:43
22	family history, age, unfortunately, the older we	10:24:46

1 get, the more likely it is to develop type 2

10:24:52

2 diabetes -- and of course, the idea was to let

10:24:56

3 individuals know that this can be implemented.

10:24:58

4 And what we stressed -- and this is a

10:25:00

5 very important point. The issue here was not

10:25:03

6 massive weight loss. In the final analysis, after

10:25:06

7 about four years of the intervention -- and I'm just

10:25:10

8 estimating what the average intervention length was

10:25:13

9 for the individuals in the trial -- there was

10:25:16

10 perhaps a 5 percent weight loss, which is not a

10:25:20

11 massive amount. But that turned out to be

10:25:23

12 fundamental in terms of giving this beneficial

10:25:26

13 58 percent decrease over subsequent years.

10:25:30

14 And I'll just point out also -- and this

10:25:33

15 is a practice that the institute would often do --

10:25:35

16 after going through all the expense and effort of

10:25:38

17 these multiple academic centers, clinical centers

10:25:42

18 around the country recruiting these patients for the

10:25:46

19 trial, by definition, the trial lasts a finite

10:25:47

20 period of time.

10:25:52

21 But we then extended, not the trial but

10:25:52

22 something called DPPOS, the Diabetes Prevention

10:25:56

1 Program outcome study, with the goal of following 10:26:00
2 these patients longer term, how durable would this 10:26:04
3 period of prevention of type 2 diabetes be. What 10:26:09
4 other outcomes, if any, in terms of cardiovascular 10:26:12
5 disease, kidney disease, might be discerned. 10:26:16

6 And there have been a series of 10:26:19
7 publications over the years; actually, most of them 10:26:22
8 subsequent to my leaving the NIH in 2006. 10:26:24

9 Q When was the last time you treated a 10:26:36
10 patient with type 2 diabetes? 10:26:39

11 A I should stress that in coming to the 10:26:42
12 Albert Einstein College of Medicine as dean in 2006, 10:26:45
13 I ceased two of my former activities. I ceased any 10:26:50
14 direct responsibility for patient care, and I ceased 10:26:55
15 conducting research in my own laboratory while I was 10:26:59
16 dean. 10:27:04

17 So the answer to that question is, 10:27:05
18 certainly not since 2006, although I obtained and 10:27:08
19 continue to have a medical license in New York 10:27:14
20 state. 10:27:17

21 Q Prior to 2006, when was the last time you 10:27:19
22 were responsible for direct responsibility for 10:27:23

1	patient care?	10:27:28
2	A Let me then answer that question by	10:27:31
3	spelling out what my role was during different	10:27:36
4	stages of my career.	10:27:38
5	Of course, as a medical student,	10:27:40
6	graduating Harvard Medical School in 1971, I had	10:27:44
7	intensive responsibility for patient care.	10:27:48
8	As a intern and resident at the Mass	10:27:51
9	General Hospital, '71 to '73, intensive	10:27:56
10	responsibility for patient care.	10:27:59
11	As an endocrine fellow trainee at the	10:28:00
12	National Institutes of Health from '73 to '76, I had	10:28:05
13	direct responsibility for patient care.	10:28:08
14	In all those contexts was directly	10:28:11
15	involved in prescribing medications to an assortment	10:28:14
16	of patients with endocrine and metabolic diseases,	10:28:17
17	including diabetes.	10:28:21
18	Subsequent to '76, I was promoted within	10:28:22
19	the NIH and elected to remain there -- and I won't	10:28:25
20	go through the CV unless you want me to -- as a	10:28:30
21	senior investigator and then as a section chief,	10:28:33
22	branch chief, and as you saw eventually a scientific	10:28:36

1 director and institute director. 10:28:41

2 Throughout that period of time, I played 10:28:42
3 a supervisory role at varying levels, but the one 10:28:43
4 that's perhaps most pertinent to your question is 10:28:47
5 supervising endocrine fellows and other trainees 10:28:50
6 that we had at the NIH in their care of patients. 10:28:54

7 So I was not personally responsible for 10:28:58
8 prescribing the medication, but in clinic 10:29:01
9 conferences, in formal rounds, in all those 10:29:04
10 contexts, I was a supervising physician responsible 10:29:09
11 for the care of those patients that was directly 10:29:12
12 given by these endocrine fellows and trainees. 10:29:16

13 Q When was that? 10:29:26

14 A Essentially since becoming a senior 10:29:26
15 investigator, '76, through the entire time, even as 10:29:29
16 institute director. 10:29:33

17 And then I want to also point out that 10:29:33
18 while I said that since coming to Einstein, I gave 10:29:36
19 up my own research laboratory and certainly was not 10:29:42
20 anymore responsible directly for patient care, I 10:29:45
21 continued to play a significant supervisory role as 10:29:48
22 dean of the medical school for a variety of 10:29:54

1 individuals.

10:29:57

2 And in that supervisory role, and I'll
3 illustrate, here, Einstein and our affiliated health
4 system, Montefiore, has its own NIDDK-funded diabetes
5 center analogous to the very diabetes center at
6 Columbia that we referred to with Goland.

10:29:58

10:30:01

10:30:07

10:30:13

10:30:16

7 I was responsible for recruiting a new
8 director of that center. I was responsible for
9 appointing our current division director within the
10 department of medicine of diabetes and
11 endocrinology.

10:30:19

10:30:21

10:30:23

10:30:27

10:30:30

12 We are an important site in multicenter
13 clinical trials, such as the GRADE trial. And the
14 woman who oversaw that trial, Jill Crandall, is the
15 person I appointed to be the division director.

10:30:31

10:30:35

10:30:38

10:30:45

16 I attend our clinic where I am privy to
17 individual cases that pose either diagnostic or
18 therapeutic problems in diabetes.

10:30:48

10:30:53

10:30:57

19 And I will, if I may, look at my phone
20 for a minute just to refer to a title of a meeting
21 that I'm missing this morning.

10:31:00

10:31:02

10:31:06

22 Q No, please do not look at your phone.

10:31:08

1	A	I don't need to look at the phone. I can	10:31:11
2		just tell you what it says. Basically, what it says	10:31:13
3		is that there's the endocrine fellows conference	10:31:15
4		from 8:00 to 9:00 in the morning on Fridays, and the	10:31:18
5		one today is being given by an endocrine fellow.	10:31:21
6		And I religiously attend these and often advise the	10:31:23
7		fellows in formulating their presentation.	10:31:27
8		It's about one of the so-called	10:31:31
9		thiazolidinedione class of drugs, pioglitazone, also	10:31:32
10		trade name Actos. And what she is presenting	10:31:39
11		concerns whether, quote, that drug has been given a	10:31:43
12		bad rap.	10:31:46
13		So I'm summarizing by saying that I've	10:31:47
14		had varying increasingly responsible levels, been	10:31:51
15		involved indirectly in the oversight of both patient	10:31:55
16		care and most certainly also in the conduct of	10:32:00
17		clinical trials in diabetes.	10:32:04
18	Q	Just as another maybe ground rule, if you	10:32:08
19		could do your best to answer my question directly.	10:32:11
20		Your counsel will have an opportunity to ask you	10:32:14
21		questions later. For example, I asked when was	10:32:16
22		that, and I think you went on to give a lot of other	10:32:19

1	answers.	10:32:22
2	So, you know, we can do a back and forth,	10:32:23
3	but I would just appreciate if you try to answer my	10:32:26
4	question directly, and it will speed this whole day	10:32:28
5	along.	10:32:31
6	Is that fair?	10:32:31
7	A Understood.	10:32:32
8	Q Fair to say the last time you had direct	10:32:32
9	responsibility for treating a patient was 1976?	10:32:35
10	MR. ANSTAETT: Objection to form.	10:32:39
11	A I would say the answer is yes.	10:32:43
12	Q In 1976, what were the first-line	10:32:48
13	therapies for treating type 2 diabetes?	10:32:54
14	A Metformin didn't come online until	10:32:59
15	the '90s in the United States. So sulfonylureas	10:33:02
16	were likely the major form of therapy at that time.	10:33:08
17	And, of course, insulin, even though it's associated	10:33:11
18	with type 1 diabetes treatment, has been used and	10:33:13
19	was being used in type 2 diabetes.	10:33:17
20	Q Have you ever prescribed a GLP-1 therapy?	10:33:18
21	A As I've already indicated, personally,	10:33:23
22	no. But certainly involved in the oversight.	10:33:26

1	And here, I'm mindful of your admonition.	10:33:31
2	I have something to add, but I won't unless you	10:33:37
3	permit me.	10:33:40
4	MR. ANSTAETT: Doctor, you can answer as	10:33:40
5	you see fit.	10:33:42
6	A Absolutely. So just to give you a	10:33:43
7	concrete example. In December of 2022, at our	10:33:45
8	diabetes center grand rounds, I presented a grand	10:33:48
9	rounds on the subject of the role of	10:33:51
10	G protein-coupled receptors in the treatment of	10:33:53
11	type 2 diabetes.	10:33:57
12	And the essence of that grand rounds,	10:33:58
13	which involved my review of a lot of pertinent	10:34:00
14	literature, including the so-called SURPASS series	10:34:03
15	of trials, involved semaglutide, tirzepatide, and	10:34:06
16	other agents most definitely in the GLP-1 receptor	10:34:12
17	agonist and GIP receptor agonist class, because	10:34:16
18	these agonists used in the therapy of type 2	10:34:21
19	diabetes activate -- bind to and activate	10:34:27
20	G protein-coupled receptors.	10:34:31
21	So that is, I think, pertinent.	10:34:32
22	Q So you think it's pertinent that you --	10:34:38

1	strike that.	10:34:41
2	What are grand rounds?	10:34:42
3	A It's a term that is applied -- first of	10:34:46
4	all, rounds -- I'll try to be concise -- is a bit of	10:34:49
5	a misnomer. That really derives from the practice	10:34:55
6	historically of a lead attending physician or	10:34:59
7	visiting physician walking around to see different	10:35:01
8	patients on a ward with medical students, interns,	10:35:04
9	residents, fellows, et cetera.	10:35:09
10	But a grand round doesn't involve that	10:35:11
11	kind of ambulation. Instead, it derives the name	10:35:15
12	grand, that qualifying term, because it is very	10:35:19
13	heavily attended, often people from all over the	10:35:23
14	given medical center, and is an opportunity also to	10:35:27
15	invite noted experts from other academic medical	10:35:32
16	centers. So hence, grand rounds.	10:35:36
17	In this case, grand rounds associated	10:35:38
18	with our NIDDK-funded diabetes center at Einstein	10:35:40
19	Montefiore.	10:35:47
20	Q So it sounds a bit more like a classroom	10:35:47
21	setting.	10:35:50
22	Is that fair?	10:35:50

1	A	No, not fair. It's a large amphitheater	10:35:51
2		with easily on -- depending on the speaker, a	10:35:56
3		hundred people or more in attendance.	10:36:00
4	Q	May not a classroom setting, but a	10:36:03
5		lecture.	10:36:07
6		Is that fair?	10:36:07
7	A	Yes, yes.	10:36:08
8	Q	So you presented at one of these grand	10:36:10
9		rounds on the literature you've read on GLP-1	10:36:13
10		receptor agonists, and that's what you consider	10:36:17
11		pertinent.	10:36:20
12		Fair?	10:36:20
13		MR. ANSTAETT: Objection to form.	10:36:21
14	A	I consider it pertinent because it's	10:36:23
15		reflective of a principle, as dean of a medical	10:36:25
16		school in education, that we call lifelong learning.	10:36:30
17		Learning does not cease when you're a medical	10:36:34
18		student, an intern, a resident, a fellow.	10:36:37
19		You have to keep up with all the latest	10:36:40
20		developments. And I should stress that in preparing	10:36:42
21		for this grand rounds, I also interact with	10:36:46
22		colleagues and derive benefit from their knowledge.	10:36:50

1 So, for example, at Einstein, we have an
2 individual who heads our obesity treatment center,
3 and with regard to GLP-1 receptor agonists, I've had
4 many, many discussions with him concerning how he
5 prescribes, what the roadblocks are in obtaining
6 certain GLP-1 receptor agonists for his patients.

7 I should stress, we are in the Bronx. We
8 are not in Manhattan. We are in the Bronx. And the
9 reason I stress that is, there's some of the highest
10 incidents of type 2 diabetes in the Bronx in the
11 entire United States.

12 So we certainly -- by "we," I'm
13 inclusively saying the staff of our medical school
14 and health system. So it's not just a question of
15 passively reading some papers; it's interacting,
16 interacting at a variety of clinic conferences, and
17 really understanding what is the state of the art,
18 what are the controversies, what are the issues.

19 Q So in addition to reading literature, you
20 interact with doctors who directly treat patients
21 that --

22 A Absolutely. Absolutely.

1	MR. ANSTAETT: Just give Mr. Reich a	10:38:02
2	chance to finish his question. I know --	10:38:04
3	THE WITNESS: Sorry.	10:38:04
4	MR. ANSTAETT: -- it's easy to talk over	10:38:06
5	one another.	10:38:07
6	Q And it makes it so much tougher on Zoom	10:38:07
7	because we have the delay. So I appreciate that you	10:38:10
8	might do it once in a while, and I might do it once	10:38:12
9	in a while. But thank you.	10:38:15
10	So you have offered the opinion that most	10:38:17
11	of the uses on the Ozempic label do not fall within	10:38:25
12	the scope of the claims of the '462 patent.	10:38:28
13	Do you recall that opinion?	10:38:32
14	A I do.	10:38:33
15	Q What is your basis for that opinion?	10:38:35
16	A The claim, which is the only independent	10:38:43
17	claim of the '462 patent, is treatment of a patient	10:38:51
18	with type 2 diabetes with a 1.0 milligram dose of	10:38:56
19	semaglutide weekly.	10:39:02
20	The prescribing information for Ozempic,	10:39:09
21	which is the subject, as I understand it, of this	10:39:14
22	patent dispute and the relevance of patent '462	10:39:17

1 starts with a titration dose of 0.25 milligram for 10:39:29
2 four weeks. Then an escalation to 0.5 milligram. 10:39:36
3 These are all weekly. And that may be the 10:39:43
4 maintenance dose, which certainly does not 10:39:49
5 correspond to the 1.0 milligram dose specified in 10:39:53
6 the '462 patent. 10:39:59

7 The prescribing information does indicate 10:40:00
8 that if insufficient reduction in hemoglobin A1c is 10:40:03
9 achieved, one can then escalate after a period of 10:40:10
10 four weeks to the 1.0 milligram per week dose, and 10:40:13
11 then goes on to say that there can be a further 10:40:16
12 escalation to 2.0 milligram. Again, on a weekly 10:40:19
13 basis. 10:40:24

14 So I find that these -- or this range of 10:40:25
15 doses is not at all encompassed in claim 1 of the 10:40:30
16 '462 patent, which specifies solely the 10:40:38
17 1.0 milligram dose. 10:40:41

18 (Reporter interruption.) 10:41:08

19 THE WITNESS: Yes, 2.0. 10:41:12

20 Q Dr. Spiegel, do you know when Ozempic was 10:41:17
21 approved? 10:41:20

22 A It was approved, I believe, in late -- in 10:41:24

1 the United States in late 2017.

10:41:28

2 Q Do you understand what the maintenance
3 doses that were approved for Ozempic in 2017 were?

10:41:31

10:41:34

4 A I believe that the maintenance doses
5 approved were both the 0.5 milligram dose or the
6 1.0 milligram dose. I believe that the
7 2.0 milligram elevation was not approved until
8 subsequent years, a few years later.

10:41:40

10:41:44

10:41:50

10:41:53

10:41:58

9 Q Do you know when 2.0 was approved?

10:42:00

10 A I have to confess, it's a guess. I would
11 say perhaps 2020.

10:42:05

10:42:08

12 Q And if I told you it was 2022, you'd have
13 no reason to dispute that?

10:42:12

10:42:14

14 A No.

10:42:16

15 Q You just don't know one way or the other
16 whether it was 2020 or 2022?

10:42:17

10:42:19

17 A It's not a question of knowing one way or
18 the other. I'm uncertain about the precise date of
19 that escalated dose approval.

10:42:24

10:42:27

10:42:32

20 Q So while you might be uncertain as to the
21 precise date, you don't dispute that for a period of
22 years, the only two maintenance doses that were

10:42:36

10:42:39

10:42:42

1 approved were 0.5 milligrams and 1.0 milligrams. 10:42:44

2 Fair? 10:42:49

3 A It is fair. My only point being that 0.5 10:42:49

4 is not the same as 1.0, which is the only dose 10:42:52

5 specified in claim 1 of the contested patent. 10:42:55

6 Q Do you have an understanding as to how 10:42:59

7 many patients stay at the 0.5 milligram maintenance 10:43:02

8 dose? 10:43:06

9 A I don't. 10:43:09

10 Q Do you know what percentage of patients 10:43:12

11 on the 0.5 milligram dose need additional glycemic 10:43:14

12 control such that they escalate to the 1.0 milligram 10:43:19

13 goes? 10:43:22

14 A Where would I obtain such information? 10:43:24

15 Q I think one of the ground rules of these 10:43:31

16 is I ask the questions, you provide an answer. So 10:43:34

17 I'll repeat the question. 10:43:37

18 Do you know what percentage of patients 10:43:39

19 on the 0.5 milligram dose need additional glycemic 10:43:42

20 control such that they escalate to the 1.0 milligram 10:43:46

21 dose? 10:43:49

22 A I don't because I don't know how I would 10:43:50

1	derive that information.	10:43:54
2	Q And you have no --	10:43:56
3	(Cross-talk.)	10:43:58
4	A And particularly -- sorry. And	10:43:59
5	particularly in the United States where we don't	10:44:01
6	necessarily have national health systems and other	10:44:02
7	databases that would provide that information.	10:44:06
8	Q And you have no personal experience that	10:44:09
9	would provide you that information, correct?	10:44:11
10	A Correct.	10:44:15
11	Q Is it also correct that you have no	10:44:19
12	understanding as to which dose of Ozempic -- strike	10:44:26
13	that.	10:44:31
14	Is it also correct that you have no	10:44:31
15	understanding as to which maintenance dose of	10:44:34
16	Ozempic is most frequently prescribed?	10:44:38
17	A No, I don't.	10:44:42
18	Q In your opinion, do 100 percent of	10:44:45
19	patients need to have 1.0 milligram prescribed as	10:44:48
20	their maintenance dose for references to Ozempic to	10:44:53
21	have nexus to the '462 patent?	10:44:57
22	MR. ANSTAETT: Objection to form.	10:45:01

1 A Based on the guidance I've received -- 10:45:05
2 and so this is now a question of legal standards 10:45:07
3 because you're using a legal term, "nexus" -- it's 10:45:10
4 my understanding that, yes, it is required that a 10:45:13
5 hundred percent of patients be on a maintenance 10:45:19
6 dose, and not just a maintenance dose, be on a dose 10:45:22
7 of 1.0. There's nothing in claim 1 that discusses 10:45:26
8 titration of doses at all. 10:45:30

9 Q So is it your understanding that because 10:45:43
10 patients titrate up to 1.0, that there's no nexus 10:45:45
11 between the use of Ozempic and claim 1 of the '462 10:45:49
12 patent because they used doses besides 1.0 milligram 10:45:53
13 in that regimen? 10:45:59

14 MR. ANSTAETT: Objection to form. 10:46:01

15 A Notwithstanding being unable to give you 10:46:02
16 a percentage of individuals, it's my understanding 10:46:04
17 that there are finite numbers of individuals with 10:46:08
18 type 2 diabetes that are maintained on a 10:46:12
19 0.5 milligram per week dose. That then suggests 10:46:16
20 that that's inconsistent with claim 1 of the '462 10:46:19
21 patent. 10:46:22

22 Q If we could turn to page 16 of 10:46:30

1	Exhibit 1302.	10:46:34
2	And Dr. Spiegel, if you would like	10:46:36
3	control to scroll yourself, I think Kollin is able	10:46:38
4	to grant you that control. So please let me know.	10:46:41
5	I'm happy to have you be able to control or look at	10:46:44
6	your paper copy, whatever works.	10:46:47
7	A I'm going to be looking at the paper	10:46:48
8	copy.	10:46:50
9	Q Just so we're all looking at the same	10:46:51
10	thing, if you want to look, it will also be on the	10:46:57
11	screen. But I want you to do whatever you're most	10:46:59
12	comfortable with, okay?	10:47:01
13	A Thank you.	10:47:02
14	Q So this section III titled Legal	10:47:02
15	Standards, do you see that section?	10:47:08
16	A I do.	10:47:11
17	Q And were these legal standards provided	10:47:12
18	to you by counsel?	10:47:18
19	MR. ANSTAETT: You can answer that yes or	10:47:21
20	no.	10:47:24
21	A Yes.	10:47:24
22	Q Is it your understanding that if there is	10:47:28

1	a property that was known in the prior art, new	10:47:32
2	results related to that property are always a	10:47:37
3	difference in degree?	10:47:40
4	MR. ANSTAETT: Objection to form.	10:47:42
5	A My understanding, at least this is	10:47:50
6	articulated in my opinion, is that -- and let me	10:47:54
7	just be sure I caught -- you're talking about	10:47:58
8	unexpected results?	10:48:02
9	Q Correct.	10:48:03
10	A Was that your question?	10:48:04
11	My opinion, as stated in the reply, is	10:48:06
12	that a difference in degree is not sufficient to	10:48:09
13	establish unexpected results. It really would need	10:48:12
14	to be a difference in kind, as opposed to degree.	10:48:15
15	Q And what is it you understand a	10:48:19
16	difference in kind to be?	10:48:21
17	A My understanding is that there should be	10:48:26
18	an entirely new effect of the relevant dose of the	10:48:29
19	drug in question that goes beyond merely exceeding	10:48:38
20	in degree prior art.	10:48:46
21	And if I can be more concrete, I would	10:48:48
22	agree that in head-to-head studies, certain doses of	10:48:53

1 semaglutide give a greater reduction in hemoglobin 10:48:57
2 A1c than certain doses of liraglutide. But I 10:49:02
3 consider those differences in degree as opposed to 10:49:06
4 differences in kind, and hence, not unexpected 10:49:08
5 results. 10:49:12

6 Unexpected results -- and may I give an 10:49:14
7 illustration in terms of a difference in kind? 10:49:17

8 Q Sure. 10:49:23

9 (Cross-talk.) 10:49:24

10 A You're nodding. 10:49:24

11 Q Yeah, please just -- 10:49:26

12 A Okay. Are you familiar with -- I'm not 10:49:28
13 asking the questions, so let me just state. 10:49:32

14 Bariatric surgery has been performed in individuals 10:49:35
15 who are not only obese but have type 2 diabetes. 10:49:40

16 Some of those individuals see a relief 10:49:44
17 from their type 2 diabetes, even before having 10:49:49
18 dramatic weight loss. So within a period of months, 10:49:55
19 let's say, as opposed to years. 10:49:58

20 That would be -- if that was achieved 10:50:01
21 with a pharmacologic therapy for type 2 diabetes, 10:50:05
22 reversion from established type 2 diabetes to normal 10:50:09

1 glycemia, I might consider that a difference in 10:50:13

2 kind. 10:50:17

3 Q What if the magnitude of the increase in 10:50:23

4 a relevant property -- let me withdraw that. 10:50:27

5 What do you consider some of the known 10:50:33

6 properties here for therapies for type 2 diabetes? 10:50:35

7 MR. ANSTAETT: Objection to form. 10:50:41

8 A Two things are pertinent. 10:50:44

9 First -- and here I'm really speaking 10:50:46

10 from the legal standards perspective -- it's my 10:50:50

11 understanding -- and I direct you to footnote 3 on 10:50:53

12 page 17, because when I use those terms such as 10:50:58

13 "it's my understanding" or "I am informed" or "I 10:51:04

14 understand," I'm reflecting the fact that that 10:51:06

15 represents my understanding achieved as a result of 10:51:09

16 guidance with regard to legal standards. 10:51:14

17 So claim 1 of the '462 patent makes no 10:51:16

18 claim to any degree of efficacy. And I think that 10:51:23

19 that's very pertinent to your question. 10:51:27

20 So even dramatic improvement in reduction 10:51:31

21 of hemoglobin A1c is not really encompassed in 10:51:35

22 claim 1 of the contested patent. 10:51:39

1 But the other point I would make is that 10:51:43
2 there's a spectrum of the efficacy of GLP-1 receptor 10:51:48
3 agonists. And that's actually reflected in one of 10:51:56
4 the documents that we cited, which is the 2023 10:52:00
5 American Diabetes Association standards and guidance 10:52:04
6 for pharmacologic therapy of type 2 diabetes, in 10:52:10
7 which GLP-1 receptor agonists are stratified with 10:52:15
8 regard to intermediate, high, and very high 10:52:19
9 efficacy. 10:52:24

10 And to me, that really establishes or 10:52:25
11 reflects -- so, for example, liraglutide is in the 10:52:27
12 high category; semaglutide is in the very high 10:52:31
13 category. 10:52:34

14 To me, that adjective "very high" as 10:52:35
15 opposed to "high" is a difference in degree, not a 10:52:37
16 difference in kind. 10:52:41

17 Q You recall that you've offered several 10:52:58
18 opinions as to nexus. 10:53:00

19 Is that fair? 10:53:01

20 A Yes, that is fair. 10:53:02

21 Q Do you understand evidence of objective 10:53:03
22 indicia can have nexus to more than one patent? 10:53:09

1	MR. ANSTAETT: Objection to form.	10:53:12
2	A What I understand is that in order for	10:53:20
3	the objective indicia or secondary considerations to	10:53:22
4	have weight in establishing the validity, in this	10:53:27
5	case of the '462 patent, there needs to be -- and	10:53:30
6	again, this is a term I've been informed about --	10:53:38
7	it's my understanding that there needs to be a nexus	10:53:41
8	between Ozempic as it's prescribed and the claim 1	10:53:44
9	of the '462 patent. That's my understanding about	10:53:49
10	nexus.	10:53:52
11	Q Throughout your declaration, you discuss	10:53:55
12	other patents.	10:53:57
13	Do you recall that?	10:53:58
14	A I do.	10:53:59
15	Q Okay. And you offer opinions that those	10:54:00
16	other patents also cover Ozempic.	10:54:05
17	Do you recall those opinions?	10:54:07
18	A I do.	10:54:09
19	Q And then throughout your report -- we can	10:54:10
20	go there if it's helpful, but you conclude that	10:54:15
21	because multiple patents cover Ozempic, there's no	10:54:19
22	nexus for the objective indicia related to the use	10:54:21

1 of Ozempic with the '462 patent.

10:54:26

2 Is that fair?

10:54:28

3 MR. ANSTAETT: Objection to form.

10:54:30

4 A I'm not sure it's fair. But I want to
5 just illustrate my opinion with a concrete example,
6 if I may.

10:54:32

10:54:37

10:54:41

7 Q What's not fair about the
8 characterization that I offered?

10:54:46

10:54:48

9 A It's too vague.

10:54:53

10 And the concrete example concerns
11 satisfying a long-felt unmet need. This is one of
12 the secondary considerations cited by Dr. Goland in
13 the affirmative for Ozempic.

10:54:55

10:54:59

10:55:07

10:55:11

14 The pertinence of the other patents that
15 we've been discussing and the patents that are
16 listed and enumerated in my reply, these patents
17 encompass -- the '343 patent, the '122 patent --
18 they encompass semaglutide in various of the claims
19 for the treatment of type 2 diabetes.

10:55:16

10:55:19

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10:55:33

10:55:37

10:55:44

20 The '343 explicitly covers semaglutide.

10:55:47

21 The '122 titled Acylated GLP-1 Peptides, covers a

10:55:51

22 class of acylated GLP-1 peptides, of which

10:55:58

1 semaglutide clearly is one. 10:56:02

2 That, which I take to be a so-called 10:56:03
3 composition of matter patent illustrated by the 10:56:06
4 relevant structures with which I am familiar in some 10:56:09
5 detail, could be considered, as articulated in my 10:56:14
6 reply, as blocking patents. 10:56:18

7 They would have precluded other persons 10:56:21
8 of ordinary skill in the art with an interest in 10:56:24
9 making such type 2 diabetes therapeutic from 10:56:26
10 proceeding because of those so-called blocking 10:56:29
11 patents. 10:56:32

12 Hence, the long-felt unsatisfied need was 10:56:33
13 blocked by the Novo patents in question, '343 and 10:56:42
14 '122. 10:56:48

15 So I don't think, given the existence of 10:56:48
16 those patents, that one can argue that Ozempic, 10:56:49
17 based on the '462 patent alone, satisfied a 10:56:54
18 long-unmet need. 10:57:01

19 Q So is it your opinion that Ozempic 10:57:05
20 satisfied a long-felt need, but it's not 10:57:07
21 attributable to the '462 patent; it might be 10:57:10
22 attributable to, for example, the '343 patent? 10:57:12

1 MR. ANSTAETT: Objection to form. 10:57:16

2 A No. What I'm saying is that you cannot 10:57:17

3 argue that the '462 patent is valid because of the 10:57:20

4 secondary consideration of long-felt unmet need, 10:57:27

5 given that blocking patents prevented other 10:57:31

6 individuals from satisfying that need by 10:57:35

7 synthesizing relevant competitor compounds. 10:57:38

8 Q Do the blocking patents satisfy the 10:57:58

9 long-felt unmet need? 10:58:02

10 MR. ANSTAETT: Objection to form. 10:58:05

11 A My understanding of the blocking patents 10:58:07

12 is that they refer to structures of acylated GLP-1 10:58:09

13 peptides, in the case of '343, semaglutide 10:58:14

14 specifically; in the case of '122, a class of GLP-1 10:58:18

15 acylated peptides that would include GLP-1. 10:58:22

16 They do specify for treatment of type 2 10:58:26

17 diabetes, but they don't specify doses, they don't 10:58:29

18 specify a prescribing regimen. 10:58:31

19 So no. 10:58:34

20 Q Why would those patents need to specify a 10:58:44

21 dose? 10:58:48

22 MR. ANSTAETT: I'm sorry, I didn't 10:58:54

1 realize Mr. Reich was done with his question.

10:58:55

2 Objection to form.

10:58:58

3 You can answer.

10:58:59

4 A I'm not saying they have to specify a
5 dose. You asked whether they would meet this
6 long-unsatisfied need, and merely by synthesizing
7 the compound and showing a structure for it, to me,
8 that's insufficient.

10:58:59

10:59:02

10:59:06

10:59:12

10:59:17

9 Q And why is it insufficient, in your
10 opinion?

10:59:21

10:59:26

11 MR. ANSTAETT: Objection to form.

10:59:26

12 A In my opinion, it's insufficient because
13 it doesn't teach how to practice the use of that
14 compound in the therapy of type 2 diabetes.

10:59:27

10:59:29

10:59:33

15 Q And why doesn't it teach how to practice
16 the use of that compound in the therapy of type 2
17 diabetes?

10:59:40

10:59:42

10:59:48

18 A Because it doesn't specify a dose or time
19 of administration.

10:59:48

10:59:51

20 Q Does claim 1 of the '462 patent teach how
21 to practice the use of semaglutide to treat type 2
22 diabetes?

11:00:05

11:00:08

11:00:16

1	MR. ANSTAETT: Objection to form.	11:00:16
2	A What claim 1 specifies is a dose --	11:00:18
3	single dose, 1.0 milligrams, and a timing of	11:00:23
4	administration, namely, weekly.	11:00:28
5	So that's what it teaches.	11:00:31
6	Q And you had said previously that the '122	11:00:41
7	and '343 patents do not teach how to practice the	11:00:45
8	use of that compound in the therapy because they	11:00:48
9	don't specify a dose or a time of administration.	11:00:51
10	Do you recall that testimony?	11:00:54
11	A I do.	11:00:55
12	Q And claim 1 of the '462 patent does	11:00:56
13	specify a dose and a timing of administration,	11:01:00
14	correct?	11:01:04
15	A Correct. But not the dose that	11:01:07
16	corresponds to the prescribing information, which I	11:01:11
17	again stress includes a maintenance dose of	11:01:16
18	0.5 milligrams.	11:01:19
19	Q If you could turn to paragraph 260 of	11:01:30
20	your report. It's on page 94, if that helps. Can	11:01:32
21	you let me know when you're there, please.	11:01:47
22	A 264, you said?	11:01:49

1	Q	Sorry, 260.	11:01:51
2	A	260. Be right with you.	11:01:54
3	Q	Are you there?	11:02:07
4	A	I am.	11:02:16
5	Q	And you write that, there is no nexus	11:02:17
6		between semaglutide once weekly 1.0 milligram dose,	11:02:20
7		and the asserted evidence of unexpected results	11:02:25
8		because the product asserted to underlie the offered	11:02:28
9		unexpected results (Ozempic) embodies claims from	11:02:34
10		several of patent owner's patents.	11:02:35
11		Do you see that?	11:02:38
12	A	I do.	11:02:38
13		MR. ANSTAETT: I want to just note that	11:02:40
14		you left out the last bit.	11:02:42
15	Q	And it finishes, and those patents do not	11:02:50
16		generally cover the same invention.	11:02:53
17		Do you see that?	11:02:54
18	A	Yes.	11:02:56
19	Q	Could you please explain your opinion	11:02:59
20		here.	11:03:02
21		MR. ANSTAETT: I'll object to form.	11:03:10
22		But you can answer.	11:03:12

1 THE WITNESS: Okay. 11:03:15

2 A It's my opinion, based on the legal 11:03:19

3 standards I've been instructed in, that the 11:04:16

4 existence of the '343 and '122 patents, and their 11:04:19

5 claims, which encompass semaglutide and its use to 11:04:23

6 treat diabetes, in essence preempts the '462 patent 11:04:26

7 and -- because it already has claims that overlap 11:04:36

8 with claim 1 of the '462 patent. 11:04:43

9 And the overlap does not need to be 11:04:49

10 total. The distinguishing feature of the '462 11:04:53

11 patent includes the specification of a dose and 11:04:57

12 timing of administration. 11:05:00

13 But nonetheless, these pre-existing '343 11:05:03

14 and '122 patent do both have claims that are 11:05:06

15 directed to semaglutide and its use to treat 11:05:09

16 diabetes. 11:05:12

17 So this was the basis for my saying that 11:05:13

18 there's no nexus between semaglutide once weekly, 11:05:16

19 1 milligram dose, and the asserted evidence of 11:05:21

20 unexpected results. 11:05:26

21 Q So is it your opinion that because there 11:05:27

22 are multiple patents that cover Ozempic, there can 11:05:30

1 be no nexus between Ozempic and the claims of the 11:05:32

2 '462 patent? 11:05:37

3 MR. ANSTAETT: Objection to form. 11:05:39

4 A I think the issue of unexpected results, 11:05:44

5 again, in my opinion, has more to do with what we 11:05:50

6 discussed earlier about degree versus kind in terms 11:05:55

7 of the results and whether they'd be unexpected, and 11:06:00

8 it has to do with the comparisons to prior art, not 11:06:04

9 only the issue of these patents, but the existence 11:06:07

10 of liraglutide. 11:06:10

11 And most particularly, the existence of 11:06:13

12 liraglutide as an effective treatment for type 2 11:06:15

13 diabetes, when administered not at the 1.2 milligram 11:06:18

14 dose per day, which is what Dr. Golland and the 11:06:22

15 SUSTAIN trial consistently refer to, but the more 11:06:27

16 effective 1.8 milligram dose. 11:06:30

17 So that's the basis of my claiming the 11:06:33

18 unexpected results is not strong evidence that's 11:06:37

19 been provided. 11:06:42

20 Q Paragraph 260 is about nexus, correct? 11:06:45

21 A Yes. 11:06:50

22 Q You're not discussing liraglutide of 11:06:51

1 1.2 milligrams in that paragraph.

11:06:54

2 Fair?

11:06:56

3 A Yes.

11:06:57

4 Q So in paragraph 260, the opinion you've
5 offered there, is it your opinion that because there
6 are multiple patents that cover Ozempic, there can
7 be no nexus between Ozempic and the claims of the
8 '462 patent?

11:07:00

11:07:04

11:07:07

11:07:09

11:07:13

9 MR. ANSTAETT: Objection to form.

11:07:15

10 A I'll just -- I'll not restate what it
11 says. I stand by what it says. That was what was
12 specified in paragraph 260.

11:07:18

11:07:21

11:07:26

13 Q That was what -- what was specified in
14 paragraph 260?

11:07:28

11:07:37

15 A Do you want me to read 260?

11:07:39

16 Q I'm trying to understand the opinion you
17 offered in paragraph 260. So --

11:07:41

11:07:44

18 A My opinion is based on the assertion of
19 unexpected results already embodies claims from
20 previous patents.

11:07:48

11:07:52

11:07:58

21 So the -- there's no nexus with the
22 claim 1 of '462 because these previous patents

11:07:59

11:08:04

1 already encompassed the use of the same compound,
2 semaglutide, to treat type 2 diabetes.

3 So why would there be unexpected results?
4 They're not unexpected.

5 Q Do you understand nexus and unexpected
6 results to be the same concept?

7 MR. ANSTAETT: Objection to form.

8 A My understanding is that in order to draw
9 a conclusion about unexpected results, there needs
10 to be nexus between the claim in the patent and the
11 actual drug that's being prescribed, in this case
12 Ozempic.

13 Q So is it fair, then, you understand that
14 unexpected results and nexus are not the same thing?

15 A Of course.

16 Q Okay. So in your opinions on nexus, was
17 it your opinion that because there are multiple
18 patents that cover Ozempic, there can be no nexus
19 between Ozempic and the claims of the '462 patent?

20 MR. ANSTAETT: Objection, form, and asked
21 and answered.

22 A I've already answered the question.

1	Q	What was the answer that you offered?	11:09:36
2		MR. ANSTAETT: Same objections.	11:09:42
3	A	The previous patents which claim	11:09:43
4		semaglutide for treatment of type 2 diabetes preempt	11:09:47
5		drawing the conclusion of unexpected results from	11:09:53
6		the once weekly 1 milligram dose of semaglutide	11:10:00
7		that's claimed in claim 1 of the '462 patent.	11:10:03
8		MR. REICH: Okay. I think we can go off	11:10:10
9		the record and take a break.	11:10:12
10		(Recess from 11:12 a.m. until 11:21 a.m.)	11:12:53
11	BY MR. REICH:		11:21:42
12	Q	Dr. Spiegel, did you look at any of your	11:21:50
13		notes on the break?	11:21:52
14	A	I did not. I looked at the -- my reply.	11:21:53
15	Q	Did you discuss the substance of your	11:22:00
16		testimony with counsel during the break?	11:22:02
17	A	Absolutely not.	11:22:04
18	Q	If you could turn to page 41 of your	11:22:07
19		declaration. It's paragraph 110. Let me know when	11:22:11
20		you're there, please.	11:22:16
21	A	I'm there.	11:22:28
22	Q	Can you explain what you meant by, type 2	11:22:29

1 diabetes is fundamentally distinct and can be 11:22:31

2 addressed by diet and exercise alone? 11:22:34

3 A Yes, I can. 11:22:41

4 Here, I am alluding to the textbooks of 11:22:43
5 medicine, standard texts, Harrison in this case, and 11:22:49
6 the first line of treatment -- and this is also 11:22:55
7 exemplified by the guidelines from the American 11:22:59
8 Diabetes Association -- is diet and exercise as the 11:23:03
9 initial step in trying to address a patient with 11:23:06
10 type 2 diabetes. The initial step. 11:23:12

11 Q And how is it that diet and exercise 11:23:16
12 treat type 2 diabetes? 11:23:19

13 A The pathophysiology of type 2 diabetes is 11:23:21
14 fundamentally an imbalance between the ability of 11:23:34
15 insulin to exert its effect, so-called insulin 11:23:37
16 resistance, and the ability of the beta cells in the 11:23:39
17 islets of the pancreas to secrete insulin. 11:23:45

18 By having a proper diet and performing 11:23:49
19 appropriate exercise -- and we're not talking about 11:23:55
20 marathons here, and this was exemplified in the 11:23:57
21 Diabetes Prevention Program trial that I told you, 11:24:01
22 although that's prediabetes -- you restore some 11:24:04

1 degree of insulin sensitivity, hence putting less

11:24:08

2 stress on the beta cells to secrete insulin.

11:24:13

3 So in a subset of individuals, diet and
4 exercise alone will be sufficient to bring them back
5 into metabolic balance.

11:24:18

11:24:20

11:24:23

6 Q So by reducing the patient's weight, you
7 treat the patient's type 2 diabetes?

11:24:26

11:24:29

8 MR. ANSTAETT: Objection to form.

11:24:34

9 A It is not merely a question of weight.

11:24:35

10 As I've stressed, it's certainly not exorbitant

11:24:37

11 amounts of weight loss, 10, 20 percent of body

11:24:42

12 weight. As little as 5 percent can make a

11:24:46

13 difference.

11:24:48

14 But yes, some degree of weight loss has a
15 beneficial effect on the issue of insulin
16 sensitivity and hence on the ability of the pancreas
17 to have sufficient insulin to achieve euglycemia.

11:24:51

11:24:55

11:24:59

11:25:03

18 Q How effective is diet and exercise alone?

11:25:23

19 MR. ANSTAETT: Objection to form.

11:25:28

20 A Depends on how far along the patient is
21 in the spectrum. And this leads me to just point
22 out that a substantial number of individuals have

11:25:31

11:25:37

11:25:40

1 undiagnosed diabetes. They lack overt symptoms and 11:25:45
2 have never presented to a physician for having 11:25:52
3 formal testing. 11:25:56

4 So if you have someone like that with 11:25:57
5 perhaps even several years of established diabetes, 11:26:00
6 it's unlikely that diet and exercise alone will 11:26:04
7 restore euglycemia. 11:26:08

8 Q Earlier you had distinguished between 11:26:14
9 5 percent weight loss versus 10 to 20 percent weight 11:26:18
10 loss. 11:26:21

11 Do you recall that? 11:26:21

12 A I recall that in the context of this 11:26:22
13 clinical trial that we've referred to, the DPP, 11:26:27
14 Diabetes Prevention Program. The degree of weight 11:26:32
15 loss achieved in the individuals with the intensive 11:26:34
16 lifestyle intervention was on the order of 5 percent 11:26:37
17 on average, and that was sufficient to achieve a 11:26:40
18 58 percent reduction in subsequent development of 11:26:44
19 type 2 diabetes. 11:26:48

20 Q And you distinguished that 5 percent 11:26:51
21 weight loss to what you referred to as exorbitant 11:26:53
22 weight loss of 10 to 20 percent. 11:26:56

1 Do you recall that just a few moments 11:26:58
2 ago? 11:27:00

3 A I do. And perhaps exorbitant -- I'm 11:27:01
4 again talking about the magnitude of change. The 11:27:04
5 ability of lifestyle intervention to create weight 11:27:11
6 loss, sustained weight loss, that is, over a period 11:27:15
7 of more than a year or so, is limited to the range 11:27:19
8 of 5 percent. 11:27:24

9 Q Is a weight loss of 10 to 20 percent of 11:27:40
10 body weight a greater benefit for patients with 11:27:43
11 type 2 diabetes? 11:27:47

12 MR. ANSTAETT: Objection to form. 11:27:47

13 A I think focusing solely on that parameter 11:27:48
14 is inappropriate. While weight and degree of weight 11:27:52
15 loss is one component, there are other components. 11:27:56

16 And harking back to what I said about 11:28:00
17 pathophysiology, the weight and the degree of weight 11:28:03
18 loss impinges on the pathophysiology of diabetes 11:28:08
19 largely with respect to the insulin resistance or 11:28:11
20 sensitivity part of the equation. 11:28:15

21 But the individual also will vary with 11:28:18
22 regard to the ability of the pancreas, the eyelet 11:28:20

1 beta cells, to compensate.

11:28:25

2 So an individual with very, very capable
3 eyelet cells, you can have, in many cases, even
4 extreme obesity and not have diabetes.

11:28:27

11:28:32

11:28:36

5 Winston Churchill comes to mind.

11:28:40

6 Q In your opinion, has diet and exercise
7 satisfied the long-felt need for therapy for
8 diabetes?

11:28:49

11:28:53

11:28:57

9 MR. ANSTAETT: Objection to form.

11:28:57

10 A No. I never stated that.

11:28:58

11 Q So beyond diet and exercise, there was
12 still a need for a type 2 diabetes therapy?

11:29:00

11:29:03

13 MR. ANSTAETT: Objection to form.

11:29:08

14 A As I've indicated, historically, there
15 have been a number of treatments developed over the
16 years, and this is all discussed in my reply in the
17 background statement, going from the history of
18 insulin, sulfonylureas, on to metformin, DPP-4
19 inhibitors, and eventually GLP-1 receptor agonists,
20 just to name a few.

11:29:14

11:29:17

11:29:19

11:29:21

11:29:24

11:29:31

11:29:36

21 Q Which, if any, of those therapies
22 satisfied a long-felt need for an improved therapy

11:29:43

11:29:45

1 for type 2 diabetes?

11:29:49

2 MR. ANSTAETT: Objection to form.

11:29:50

3 A I think it would be inappropriate to
4 single out any one of these because that's going to
5 be a moving target as a function of where in the
6 history of therapeutics development for type 2
7 diabetes we are.

11:29:54

11:29:56

11:30:01

11:30:04

11:30:10

8 For example, metformin, which was
9 approved in the United States in the '90s, being an
10 oral medication, became the first-line treatment
11 after diet and exercise.

11:30:10

11:30:12

11:30:18

11:30:23

12 And so again, it's a value judgment. One
13 might say that it met a long-felt unsatisfied need
14 in the sense of a convenient oral medication, albeit
15 with potentially some GI side effects that was
16 superior to diet and exercise alone.

11:30:26

11:30:28

11:30:33

11:30:37

11:30:41

17 But as I said, I would not single out any
18 one of these treatments. There's a continuum of the
19 development of these different agents.

11:30:43

11:30:46

11:30:50

20 And, for example, the SGLT2 inhibitors
21 comes to mind. Quite an important advance in
22 treatment of type 2 diabetes.

11:30:51

11:30:55

11:30:58

1	Q	When were SGLT2 inhibitors released?	11:31:07
2	A	In the early 2010s.	11:31:13
3	Q	In paragraph 111 you write, any degree of	11:31:25
4		improvement in glycemic control has a benefit in	11:31:28
5		treating type 2 diabetes.	11:31:32
6		Do you see that?	11:31:33
7	A	I do see that. But you omitted the	11:31:45
8		second clause in that sentence, which would be,	11:31:48
9		normalization of glucose levels is not strictly	11:31:54
10		necessary to slow the progression of complications	11:31:55
11		resulting from the disease.	11:31:57
12		And this leads me to stress a very	11:31:59
13		important point, if I may.	11:32:01
14		The mere correction of hyperglycemia is,	11:32:08
15		in general, not an end in itself. With the	11:32:12
16		exception of the rare, fortunately, conditions of	11:32:18
17		ketoacidosis, a condition in which there's flagrant	11:32:24
18		hypercalcemia and is life-threatening and where	11:32:29
19		instantaneous treatment is required, the sole	11:32:32
20		rationale for lowering the blood sugar on an ongoing	11:32:36
21		basis in people with type 2 diabetes is what's said	11:32:40
22		in that second clause in that sentence.	11:32:43

1 It's amply clear that the complications
2 of type 2 diabetes, both so-called microvascular and
3 macrovascular, are due to the persistent
4 hyperglycemia. So that's the goal in lowering the
5 blood sugar.

11:32:48

11:32:51

11:32:54

11:32:59

11:33:02

6 And then the sentence becomes clear, that
7 you benefit the patient, even with some degree of
8 improvement, any degree, but some substantive degree
9 of improvement, in slowing progression of the
10 complications. They don't have to be absolutely
11 normal.

11:33:03

11:33:06

11:33:12

11:33:15

11:33:19

11:33:22

12 So that's what I'm saying there.

11:33:23

13 Q What do you consider some degree of
14 improvement? Is that any numerical improvement, or
15 did you mean something else in this sentence?

11:33:40

11:33:42

11:33:45

16 A I didn't quantitate it in the sentence.
17 And if you're asking me to quantitate it now, it's
18 difficult to do. There are going to be differences,
19 again, in individuals.

11:33:50

11:33:53

11:33:58

11:34:01

20 For example, we know that there are
21 individuals more susceptible at a degree of
22 hyperglycemia to complications, possibly for

11:34:04

11:34:06

11:34:08

1 intrinsic genetic differences. 11:34:11

2 So the generality is that you want to 11:34:14

3 achieve closer to normal glycemia, as reflected in 11:34:19

4 the hemoglobin A1c, an integrated measure of your 11:34:27

5 control of glycemia in order to stave off these 11:34:30

6 complications. 11:34:34

7 But it's not a linear progression in 11:34:35

8 terms of some quantitative number of A1c and certain 11:34:40

9 complications, A. 11:34:45

10 B, it will vary from patient to patient. 11:34:47

11 There's substantial intersubject variability in that 11:34:50

12 relationship between the development of 11:34:54

13 complications and the degree of hyperglycemia. 11:34:55

14 Q If you could turn to paragraph 117 on 11:35:09

15 page 44. Let me know when you're there, please. 11:35:11

16 A Yes, I'm there. 11:35:18

17 Q You wrote that, Metformin is known to 11:35:19

18 promote moderate weight loss. 11:35:23

19 Do you see that? 11:35:25

20 A I do see it. 11:35:27

21 Q What do you consider a moderate amount of 11:35:29

22 weight loss? 11:35:31

1	A	Something less than 10 percent and	11:35:36
2		perhaps in the 2 to 5 percent range.	11:35:38
3	Q	In your opinion, metformin produced 2 to	11:35:46
4		5 percent weight loss in patients?	11:35:50
5	A	It can, and again, there's going to be	11:35:53
6		substantial intersubject variability.	11:35:56
7		Metformin, again, depending on how it's	11:35:59
8		administered and the age of individuals -- older	11:36:03
9		subjects are more susceptible to GI side effects of	11:36:09
10		metformin, and that's going to be dose limiting in	11:36:14
11		some individuals.	11:36:18
12		So the degree of weight loss will vary,	11:36:18
13		but can be in that range that I specified.	11:36:21
14		Certainly not 10 percent or higher.	11:36:24
15	Q	And is that based off -- sorry, withdraw	11:36:37
16		that question.	11:36:41
17		What is your understanding based off of?	11:36:42
18	A	It's based on the ADA guidelines. It's	11:36:47
19		based on clinical practice, discussions with	11:36:56
20		colleagues. It's pretty clear that the ADA	11:37:02
21		guidelines recommend as a first measure diet and	11:37:07
22		exercise, lifestyle intervention.	11:37:12

1 That is true in all, irrespective of 11:37:18
2 layering on additional therapeutics, if necessary. 11:37:22
3 That still is appropriate in any individual with 11:37:26
4 type 2 diabetes. 11:37:28

5 Metformin became the standard of care as 11:37:28
6 the first-line treatment because of its favorable 11:37:32
7 profile, not causing hypoglycemia, which is a very 11:37:35
8 concerning complication of some agents, and giving 11:37:40
9 some modest or moderate, as stated here, weight 11:37:46
10 loss, and helping to reduce the fasting plasma 11:37:50
11 glucose. 11:37:56

12 Q But that's not based on personal 11:37:57
13 experience treating patients, correct? 11:38:02

14 A It's based, as I've already emphasized 11:38:04
15 repeatedly, on the fact that I have not been 11:38:07
16 personally directly treating patients, but have been 11:38:11
17 very heavily involved in the oversight of endocrine 11:38:13
18 fellows who are treating such patients, 11:38:17
19 participating in clinics and clinic conferences, 11:38:19
20 interacting with colleagues who every day are seeing 11:38:22
21 such subjects using metformin. 11:38:25

22 And so that's where my knowledge base 11:38:27

1 comes from. And yes, also reading the literature. 11:38:30

2 Q Do you understand what an incretin-based 11:38:37

3 therapy is? 11:38:41

4 A I believe so. 11:38:42

5 Q What's your understanding of what an 11:38:44

6 incretin-based therapy is? 11:38:45

7 A The starting point would have to be what 11:38:49

8 is an incretin. And we can debate pronunciation. 11:38:52

9 But the upshot is -- it was observed 11:38:55

10 decades and decades ago, this is a long-standing 11:39:00

11 observation -- that an oral glucose tolerance test 11:39:03

12 in the same individual gave a response that was 11:39:09

13 better than an intravenous glucose tolerance test. 11:39:15

14 That is, giving the same subject the same glucose 11:39:19

15 load intravenously versus orally, there was some 11:39:25

16 beneficial effect of going through the GI tract. 11:39:30

17 And that was then initially speculated 11:39:32

18 and later more scientifically proven to be due to 11:39:35

19 so-called incretins, namely, gastrointestinal 11:39:41

20 epithelial cell peptides that were being secreted 11:39:46

21 that facilitated the secretion of insulin by the 11:39:52

22 beta cell and facilitated the disposal of glucose so 11:39:58

1 that the glucose tolerance test was better. That's
2 the so-called incretin effect.

3 And if I can restate what your question
4 was, incretin-based therapy, that's what you asked,
5 if that's what you asked, yes, that then focused
6 attention on what could be these gut-derived
7 peptides that had the potentially beneficial effect,
8 it immediately came to mind that these might be
9 therapeutically useful in treatment of type 2
10 diabetes.

11 Q Do all incretin-based therapies treat
12 type 2 diabetes?

13 MR. ANSTAETT: Objection to form.

14 A I would, in the interest of being
15 scientifically more precise, avoid the term
16 "incretin-based therapies." I think that that is an
17 out of date, archaic term, if I may say so.

18 So we need to get into more relevant
19 terms, what are the gut-secreted peptides possibly
20 responsible for the so-called incretin effect? Very
21 notably, glucagon-like peptide-1 receptor agonists,
22 that would be a very important class of potential

1 incretin-based therapy.

11:41:24

2 However, there is also glucose-inducible
3 insulinotropic peptide, GIP, another potential
4 incretin-based peptide.

11:41:26

11:41:29

11:41:33

5 So therapeutics -- and these are just two
6 examples. The gut is an endocrine organ. It
7 secretes many, many hormones, only some of which
8 have been sufficiently identified and characterized.

11:41:36

11:41:40

11:41:44

11:41:48

9 But clearly, the therapy using both
10 GLP-1-based receptor agonists and tirzepatide,
11 GIP-based receptor agonists has advanced
12 substantially.

11:41:50

11:41:56

11:42:03

11:42:06

13 Q Is it your opinion that every GLP-1-based
14 therapy will treat type 2 diabetes?

11:42:08

11:42:11

15 MR. ANSTAETT: Objection to form.

11:42:14

16 A Again, the problem with stating the
17 question that way is, it's too all inclusive,
18 "every." GLP-1, the native authentic peptide, the 7
19 to 37 amino acids, GLP-1, as secreted in human gut,
20 very, very difficult to imagine it being useful in
21 the therapy of type 2 diabetes, which is not to say
22 it doesn't have effects.

11:42:18

11:42:22

11:42:29

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11:42:47

11:42:51

11:42:54

1 Early studies -- and by "early," we're
2 talking, you know, early 2000s -- infused for
3 lengthy periods of time GLP-1, native GLP-1, into
4 individuals with type 2 diabetes, and very
5 beneficial effects were noted. But that's not the
6 most practical mode of administration.

7 Q I'm not sure you answered my question, so
8 I'll try again.

9 Is it your opinion that every GLP-1-based
10 therapy will treat type 2 diabetes?

11 MR. ANSTAETT: Objection to form, asked
12 and answered.

13 A It's my opinion that every GLP-1 receptor
14 agonist will have the potential to be useful in
15 treatment of type 2 diabetes to varying degrees,
16 depending on factors such as pharmacodynamics,
17 pharmacokinetics, acceptable safety profile, side
18 effects, et cetera.

19 Q Why does the safety profile matter?

20 A Safety is always a critical consideration
21 for any therapeutic. There's always a cost-benefit
22 ratio. We give cancer -- chemotherapy, which is

1 incredibly toxic and difficult. But the
2 alternative, death from metastatic cancer, suggests
3 that safety, to a degree, may be compromised.

4 In this case, it matters because type 2
5 diabetes is a chronic disease, and it may be that
6 the therapy is going to be required lifelong. So
7 safety is absolutely required.

8 Q So I'm just trying to understand the
9 answer you just gave.

10 In your opinion, because type 2 diabetes
11 is a chronic disease, safety is more important?

12 A More important than what? I'm not sure
13 what that means.

14 Q As compared to a disease that is not
15 chronic.

16 MR. ANSTAETT: Objection to form.

17 A I don't think that's the key variable,
18 except what I mean to indicate by "chronic" is that
19 there can be cumulative effects with regard to a
20 safety profile.

21 Can I illustrate that?

22 Q Please.

1 A Adriamycin, a cancer therapy, very, very
2 useful in treatment of some cases of breast cancer
3 at a certain point. But it then turned out that
4 with sufficient cumulative dosage, there was a
5 severe, severe toxicity to the heart, to the
6 myocardium.

7 So in a chronic disease, unlike even
8 cancer, you have to be sure that administered for
9 years, if not lifelong, there will not be cumulative
10 toxicity. That's an important consideration.

11 Q And if a therapy for type 2 diabetes was
12 cumulatively toxic, would you consider that to be a
13 treatment for type 2 diabetes?

14 MR. ANSTAETT: Objection to form.

15 A I would not. And that would be a
16 concern.

17 But let me give a more concrete example.

18 I said earlier that metformin was not
19 approved in the United States until the '90s. It
20 was actually approved a couple of decades before in
21 Europe.

22 And one of the concerns had to do with

1 the earliest form, which was called phenformin,
2 which could cause a catastrophic metabolic syndrome
3 called lactic acidosis.

4 And I think that experience led to
5 substantial delay, but eventually the development of
6 metformin, which is free of that toxicity, allowed
7 it to be approved in the United States and used.

8 So again, safety is a compelling issue
9 when it comes to any acceptable treatment for type 2
10 diabetes.

11 Q And how do you determine if a potential
12 therapy for type 2 diabetes is safe?

13 MR. ANSTAETT: Objection to form.

14 A If you're asking me how the FDA
15 determines safety of an agent, it's again a
16 multi-tiered process. It begins with small animal
17 studies, eventually nonhuman primate studies may be
18 necessary, and of course, ultimately human clinical
19 trials in which a Data Safety and Monitoring Board
20 is present explicitly to look for untoward effects.

21 And those are all, you know, cogent and
22 relevant things in terms of assessing safety.

1 Q Can you determine if a therapy is safe 11:48:17
2 without testing it in humans? 11:48:19

3 MR. ANSTAETT: Objection to form. 11:48:21

4 A You will certainly, and I think the FDA 11:48:25
5 will require you to, get preliminary data in animal 11:48:27
6 models of various sorts. But those are not 11:48:30
7 sufficient, and there can be unique circumstances 11:48:35
8 where humans obviously respond differently. 11:48:39

9 But let me illustrate with a very 11:48:42
10 pertinent point. 11:48:45

11 What we see the TV advertisements for 11:48:47
12 various GLP-1 receptor agonists, or hard copy 11:48:50
13 advertisements, whatever form, pharmaceutical 11:48:55
14 advertising, they refer to something called MEN2, 11:48:59
15 multiple endocrine neoplasia type 2. And in 11:49:05
16 particular, one component of MEN2, medullary 11:49:11
17 carcinoma of the thyroid. 11:49:11

18 And that is, my understanding, because in 11:49:13
19 some of the early animal toxicity studies of some of 11:49:16
20 the GLP-1 receptor agonists, medullary carcinoma of 11:49:20
21 the thyroid was observed in some rats who were 11:49:25
22 administered those agents. 11:49:27

1 But eventually, apparently, the FDA 11:49:29
2 concluded that that was a sufficient concern to put 11:49:31
3 that warning forward on labeling -- it's prominent 11:49:35
4 on the prescribing information for GLP-1 receptor 11:49:39
5 agonists -- but not sufficient to preclude approval 11:49:42
6 for use in humans. 11:49:45

7 Q Earlier you had testified, it's my 11:49:52
8 opinion that every GLP-1 receptor agonist will have 11:49:54
9 the potential to be useful in treatment of type 2 11:49:57
10 diabetes to varying degrees. 11:50:00

11 Do you recall that testimony? 11:50:02

12 A I do. 11:50:03

13 Q Why do they only have the potential to be 11:50:04
14 useful? 11:50:08

15 MR. ANSTAETT: Objection to form. 11:50:09

16 A The first illustration I gave was the 11:50:14
17 authentic native peptide, GLP-1 itself. Not 11:50:16
18 practical, given its very rapid degradation, for 11:50:22
19 ongoing treatment of individuals with type 2 11:50:27
20 diabetes. 11:50:31

21 As different modified versions of the 11:50:32
22 native GLP-1 were developed, it became apparent, and 11:50:36

1	one of the first was based on the --	11:50:42
2	(Reporter interruption.)	11:50:54
3	A -- Gila monster venom, and it's a	11:50:57
4	naturally occurring peptide in that lizard called	11:51:02
5	exendin, exendin-4. And that was one of the first	11:51:10
6	GLP-1 receptor analogs to be developed for therapy	11:51:14
7	of type 2 diabetes and ultimately was marketed but	11:51:20
8	was modified in extended release form, for example.	11:51:22
9	And so that is an example of a GLP-1	11:51:27
10	receptor agonist that was modified sufficiently to	11:51:31
11	make it practical for therapy of type 2 diabetes.	11:51:34
12	And, of course, subsequently, there have been a good	11:51:38
13	number of others.	11:51:41
14	Q You said that it has the potential, and	11:52:03
15	it sounds like you're going with frequency of	11:52:08
16	administration as the potential -- I'm trying to	11:52:10
17	understand.	11:52:10
18	When you said it has the potential to be	11:52:14
19	therapeutically effective for type 2 diabetes, what	11:52:16
20	are the variables that go into whether it will	11:52:18
21	actually be therapeutically effective?	11:52:21
22	MR. ANSTAETT: Objection to form.	11:52:24

1 A Let me restate or try to clarify what I 11:52:27
2 mean when I say "potential." 11:52:32

3 I believe it's a class effect, that is a 11:52:34
4 specific term, of all GLP-1 receptor agonists to be 11:52:38
5 beneficial in individuals with type 2 diabetes. And 11:52:44
6 that is because there are a number of physiologic 11:52:48
7 effects that the GLP-1 receptor agonists peptide, 11:52:53
8 starting with the native peptide and then 11:52:58
9 modifications has. 11:53:00

10 Those include enhancing the secretion of 11:53:02
11 insulin from the beta cells, enhancing the synthesis 11:53:06
12 of insulin in beta cells, decreasing the 11:53:10
13 counterregulatory hormone glucagon secretion from 11:53:15
14 alpha cells, delaying gastric empty, which has a 11:53:20
15 beneficial effect although can precipitate side 11:53:24
16 effects, including, at the extreme, nausea and 11:53:27
17 vomiting, and as we now know, satiety effects due to 11:53:30
18 GLP-1 receptors in the brain, in centers of the 11:53:36
19 brain that are relevant to regulating appetite. 11:53:39

20 So every GLP-1 receptor agonist, starting 11:53:42
21 with the native peptide, going through modified 11:53:46
22 versions, has the potential to be useful for all of 11:53:50

those reasons in treatment of type 2 diabetes.

Important, when I say "modified versions," of course, it's absolutely necessary to prove this can be done, with a variety of very rigorous in vitro and ultimately in vivo tests, that the modifications you've done have not in some way abrogated the intrinsic biologic activity of the GLP-1 receptor analog that is binding to its cognate receptor, and not only binding, but activating the receptor and leading to the downstream signal link that engenders physiologic effects of GLP-1.

Q Is that because the modifications might in some way impact those intrinsic features?

MR. ANSTAETT: Objection to form.

A Yes, absolutely.

The first paper I ever published as a medical student in endocrinology in 1969 described various forms of the related hormone, glucagon, and its ability to signal to increase second messenger, cyclic AMP.

And it showed that you could lop off the last two amino acids of this 29 amino acid peptide

1 and still retain some activity. But when you lopped
2 off the last six amino acids, 1 through 23, you
3 abrogated the activity.

4 By analogy, with GLP-1, 7 to 37 natural
5 peptide, there are modifications that would
6 apparently be tolerable, maybe even beneficial, we
7 can get to that, in pharmacodynamics.

8 But on the other hand, you could abrogate
9 the effect, and that would, of course, defeat the
10 purpose in terms of using it therapeutically.

11 Q Is your opinion that any dose of a GLP-1
12 administered at any frequency will treat type 2
13 diabetes?

14 MR. ANSTAETT: Objection to form.

15 A To me, that's too vague and
16 all-encompassing a question. Any dose? One
17 microgram of a particular GLP-1 receptor analog
18 might have no effect. But I believe that there will
19 be a gradation effect, a dose-response curve.

20 And so many, many doses, depending on the
21 particular -- the precise dose depends on the
22 particular relevant analog, could have effects, and

1 you would see a dose-response. 11:56:34

2 Q How do you know which doses will have an 11:56:38
3 effect? 11:56:40

4 MR. ANSTAETT: Objection to form. 11:56:41

5 A If you're asking me about drug 11:56:44
6 development, what will be standard practice in this 11:56:46
7 development will be a series of assays that are 11:56:52
8 first conducted in vitro, so to speak. You want to 11:56:56
9 assess the ability to bind to the receptor, and 11:56:59
10 there are various assays that will measure that and 11:57:02
11 the binding affinity. You want to assess the 11:57:04
12 ability to signal downstream. 11:57:07

13 You then want to move potentially to 11:57:08
14 animal studies to look at physiologic effects that 11:57:10
15 you're looking for. You, for example, could have a 11:57:13
16 mouse model or rat model with type 2 diabetes and 11:57:16
17 see what the effects are. 11:57:19

18 And so all of these would give you some 11:57:20
19 doses, but ultimately, you wouldn't necessarily be 11:57:22
20 able to extrapolate from those doses to doses in 11:57:25
21 humans. And so this is what phase 1 and phase 2 11:57:29
22 trials are all about. 11:57:33

1 Phase 1, by the way, primarily safety,
2 going back to that theme. Phase 2 could certainly
3 be looking at pharmacodynamics, pharmacokinetics,
4 and possibly efficacy.

5 Q If you could turn to paragraph 138 of
6 your declaration. It's on page 51. Let me know
7 when you're there, please.

8 Actually, I realize we've been going --

9 A I am there.

10 Q We've been going about 40 minutes. If
11 you want to take a break now, Dr. Spiegel, or we can
12 continue. We're going to go into a stretch, but I
13 know it's around lunchtime, so I just want to make
14 sure you're good with proceeding.

15 A I'm happy to proceed, but I defer to my
16 colleagues who know that I don't eat lunch, but they
17 do.

18 MR. ANSTAETT: It's up to you, Josh. We
19 can proceed if you want or -- we'll leave it in your
20 hands.

21 MR. REICH: We can go for a little bit
22 longer.

1	MR. ANSTAETT: Yeah, I wouldn't want to	11:59:46
2	go, like, another hour, but yeah.	11:59:48
3	MR. REICH: Well, do you want to --	11:59:52
4	(Cross-talk.)	11:59:58
5	MR. ANSTAETT: It's your call.	11:59:58
6	MR. REICH: Fair enough.	12:00:01
7	Q You just talked about phase 2 trials and	12:00:03
8	looking at pharmacodynamics and pharmacokinetics and	12:00:06
9	possibly efficacy.	12:00:09
10	Do you recall that?	12:00:10
11	A Yes.	12:00:11
12	Q Is it important to know that data before	12:00:12
13	you -- withdraw that.	12:00:18
14	Prior to seeing any of that data, would	12:00:22
15	you be able to tell what doses would be effective	12:00:25
16	for treating humans with any therapy?	12:00:28
17	MR. ANSTAETT: Objection to form.	12:00:34
18	A The way I would respond to that is, if	12:00:38
19	you're dealing with a class such as GLP-1 receptor	12:00:43
20	agonists, and you already have some information on	12:00:49
21	some members of the class and now you're talking	12:00:53
22	about predictions of dose in a newer member of the	12:00:56

1	class, you might be able to make an informed guess.	12:01:00
2	But that would not be necessarily definitive.	12:01:05
3	So I realize that's a bit of a vague	12:01:10
4	answer, but that's my understanding of your	12:01:12
5	question.	12:01:15
6	Q And you reviewed the specification of the	12:01:16
7	'462 patent, correct?	12:01:20
8	A Yes.	12:01:22
9	Q Did you review the figures?	12:01:23
10	A Yes.	12:01:26
11	Q And would you agree that there were	12:01:27
12	certain doses of semaglutide that were not shown to	12:01:29
13	have any significant effect on HbA1c, for example?	12:01:35
14	MR. ANSTAETT: Objection to form.	12:01:40
15	A It's my understanding that there are what	12:01:44
16	I would say very low doses of semaglutide,	12:01:48
17	relatively speaking, in the range of 0.1 milligrams,	12:01:52
18	for example, that nonetheless have an effect, a	12:01:58
19	measurable effect in terms of reduction of	12:02:00
20	hemoglobin A1c by comparison to placebo.	12:02:04
21	So as I said earlier, just to give a	12:02:08
22	ridiculous example -- and this was not documented in	12:02:11

1 things I reviewed, certainly not in '462 -- you 12:02:13
2 know, to get microgram quantities, low microgram 12:02:19
3 quantities, they wouldn't see an effect. But 12:02:24
4 there's a dose-response very clearly. 12:02:27

5 Q What do you understand "treating type 2 12:02:35
6 diabetes" to mean? 12:02:37

7 MR. ANSTAETT: Objection to form. 12:02:40

8 A I emphasized earlier that the goal of 12:02:43
9 treating type 2 diabetes is not merely glycemia 12:02:47
10 focused. Glycemia, as reflected in hemoglobin A1c, 12:02:52
11 an integrated measure of blood sugar, is a surrogate 12:02:57
12 for what you're really after, which is preventing 12:03:01
13 the microvascular and macrovascular complications. 12:03:03

14 So the goal is to achieve as low a blood 12:03:07
15 sugar as is necessary to, as far as possible, 12:03:11
16 prevent such complications, but very importantly, 12:03:15
17 without causing the reverse, hypoglycemia. 12:03:20
18 Certainly a hazard with certain forms of treatment 12:03:25
19 such as insulin. 12:03:29

20 Q You understand that claim 1 of the '462 12:03:32
21 patent requires treating type 2 diabetes. 12:03:35

22 Fair? 12:03:38

1 A I don't see the word "requires." I think
2 what it says is that it claims the use of
3 1 milligram of semaglutide administered weekly for
4 the treatment of type 2 diabetes.

5 Q So in coming to the opinions that you've
6 expressed in your declaration, you didn't understand
7 that it was a requirement that semaglutide be
8 administered for the treatment of type 2 diabetes?

9 MR. ANSTAETT: Objection to form.

10 A Insofar as the patent is relevant at all
11 to Ozempic, yes. For example, let me state the
12 negative. It is not in the patent '462 for
13 treatment of obesity and weight loss. It's for the
14 treatment of type 2 diabetes.

15 Q And within the context of the patent,
16 what do you understand it to mean when the patent
17 claims "treating type 2 diabetes"? What do you
18 understand that term to mean?

19 A That this will be a useful agent in
20 treating type 2 diabetes.

21 Q And how do you determine whether it's a
22 useful agent for treating type 2 diabetes?

1 A Interestingly, efficacy is not specified
2 in the claim. Nonetheless, as I read the '462
3 patent, it certainly illustrated with figures which
4 show the dose-response for both weight loss as well
5 as reduction in hemoglobin A1c with varying doses of
6 semaglutide and comparison to two doses of
7 liraglutide.

8 Q So in your opinion, what is -- what does
9 it mean to treat type 2 diabetes with semaglutide?
10 What is required for it to be a treatment of type 2
11 diabetes?

12 MR. ANSTAETT: Objection to form.

13 A What's required is that there be an
14 acceptable safety and tolerability profile -- and
15 this is not reflected in the patent, this is me, as
16 a physician -- and that it be effective at a given
17 dose and a given frequency of administration in
18 lowering the hemoglobin A1c.

19 Q If you could turn to paragraph 55 on
20 page 26, just so we're looking at the claim.

21 A You lost me for a moment. You had
22 directed me to paragraph 138 on page 51, and I don't

1	think we ever did that. Forget that, okay. So now	12:06:35
2	you're telling me page 56?	12:06:38
3	Q Page 26, paragraph 55. Let me know when	12:06:41
4	you're there, please.	12:07:02
5	A I will.	12:07:03
6	Okay.	12:07:04
7	Q And do you see it says, A method for	12:07:06
8	treating type 2 diabetes, comprising administering	12:07:08
9	semaglutide once weekly in an amount of	12:07:11
10	1.0 milligrams to a subject in need thereof?	12:07:14
11	A I do see that.	12:07:18
12	Q Okay. And when it says it's a method for	12:07:19
13	treating type 2 diabetes, what I'm trying to	12:07:24
14	understand is, what do you understand "treating" to	12:07:27
15	mean in the context of claim 1?	12:07:31
16	A My understanding is that administering	12:07:38
17	this dose with this frequency will be predicted to	12:07:42
18	be beneficial to a subject with type 2 diabetes as	12:07:48
19	reflected in the reduction of hemoglobin A1c to a	12:07:50
20	certain degree, efficacy not specified.	12:07:54
21	Q Is it any numerical reduction of HbA1c?	12:07:58
22	Is that a treatment, in your opinion?	12:08:05

1	A	It could be, yes.	12:08:06
2	Q	So 0.0001 percent reduction in HbA1c, the	12:08:08
3		patient is treated -- the patient's type 2 diabetes	12:08:15
4		is treated, in your opinion?	12:08:17
5	A	Forgive my Latin, but you're posing a	12:08:20
6		reductio ad absurdum. No one would consider that	12:08:24
7		minimal a reduction as an effective treatment.	12:08:30
8		What I'm stressing, though, is that a	12:08:36
9		particular level of efficacy is not stated in this	12:08:38
10		claim. And what I'm also stating is that in	12:08:42
11		individuals with type 2 diabetes, some degree of	12:08:46
12		reduction, it's a spectrum, certainly not 0.001	12:08:49
13		reduction, but some degree of reduction.	12:08:55
14		There's not some magic threshold which	12:08:58
15		says, oh, this is a treatment, whereas just a few	12:09:01
16		percent below that would not be beneficial.	12:09:05
17		So that's what I'm stressing.	12:09:07
18	Q	When you're saying it has to be a	12:09:09
19		beneficial effect, is that a clinically meaningful	12:09:14
20		impact? I'm trying to understand, what is it --	12:09:17
21		when you read this claim and came to your opinions,	12:09:19
22		what was your understanding of "treating type 2	12:09:22

1 diabetes"? What did that encompass? 12:09:26

2 MR. ANSTAETT: Objection to form, asked 12:09:29

3 and answered. 12:09:31

4 A As I've already stated, the goal of 12:09:31

5 treating type 2 diabetes is to lower the hemoglobin 12:09:33

6 Alc, a reflection of the blood sugar, in the attempt 12:09:36

7 to help prevent future micro and macrovascular 12:09:42

8 complications. 12:09:47

9 So to the extent that treating a subject 12:09:48

10 with type 2 diabetes with 1 milligram once weekly 12:09:52

11 would create such an effective reduction of 12:09:56

12 hemoglobin Alc, yes, that would be a method for 12:10:01

13 treating type 2 diabetes. 12:10:03

14 But that's not what's at issue. What's 12:10:06

15 at issue are the blocking patents we've discussed, 12:10:08

16 the failure to compare to prior art, the fact that 12:10:11

17 there are other effective treatments that preclude 12:10:14

18 the secondary considerations, unexpected results of 12:10:19

19 satisfying a long-felt unmet need, and certainly the 12:10:25

20 praise and the skepticism. 12:10:31

21 These were the secondary considerations 12:10:33

22 which I read in the Goland declaration, and these 12:10:36

1 are the ones that I believe are not effectively 12:10:39
2 addressed with regard to claim 1 of the '462 patent. 12:10:44

3 Q If 1.0 milligrams administered once 12:10:55
4 weekly was intolerable, would you consider that to 12:10:59
5 be a treatment for type 2 diabetes? 12:11:02

6 A Again, a reductio ad absurdum. 12:11:04

7 MR. ANSTAETT: I'm sorry, I just wanted 12:11:08
8 to lodge a form objection. 12:11:08

9 But you can answer. 12:11:08

10 THE WITNESS: Yes, yes. 12:11:10

11 A No one would consider that to be the 12:11:10
12 case. But again, this is not an all-or-nothing 12:11:14
13 phenomenon. There are clinical trials and reports 12:11:18
14 of clinical trials where significant numbers of 12:11:21
15 subjects treated, for example, with semaglutide 12:11:25
16 could not tolerate it and had to go off of it. 12:11:28

17 That's the case for other GLP-1 receptor 12:11:30
18 agonists, because of the aforementioned likely 12:11:33
19 effect on delaying gastric emptying and the 12:11:36
20 interaction between that effect and the particular 12:11:41
21 individual. 12:11:44

22 Q If 1.0 milligrams of semaglutide was 12:11:48

1 toxic, would you consider that to be a treatment for 12:11:52
2 type 2 diabetes? 12:11:54

3 MR. ANSTAETT: Objection to form. 12:11:56

4 A I would not, because I would not want to 12:11:59
5 administer something that is toxic, again, depending 12:12:02
6 on how one quantifies that and characterizes that to 12:12:06
7 subjects with type 2 diabetes. 12:12:14

8 Q Can you turn to page 100, footnote 18. 12:12:29
9 And just let me know when you're there, please. 12:12:32

10 A Okay. Yes. 12:12:34

11 Q You say, The claimed methods also do not 12:12:49
12 facially require either safety or tolerability. 12:12:52

13 Do you see that? 12:12:54

14 A I do. 12:12:55

15 Q Does that mean you agree they're 12:12:55
16 implicitly required? 12:13:01

17 MR. ANSTAETT: Objection to form. 12:13:03

18 A What I meant by that is that the '462 12:13:17
19 patent doesn't address issues of safety or 12:13:19
20 tolerability. And that's all I meant by that, the 12:13:20
21 fact that it doesn't address it. 12:13:26

22 I think I was responding to Dr. Goland's 12:13:31

1 declaration there. That is the reason for that 12:13:35
2 footnote. Her declaration made a huge point about 12:13:38
3 the safety and tolerability of Ozempic, and that's 12:13:41
4 not specified in the '462 patent. That's all I was 12:13:49
5 saying with this footnote. 12:13:53

6 Q So while it's not specified, you don't 12:14:06
7 dispute that safety and tolerability is a factor as 12:14:08
8 to whether a patient can be treated with Ozempic 12:14:11
9 administered once weekly at 1.0 milligrams. 12:14:14

10 Fair? 12:14:18

11 MR. ANSTAETT: Objection to form. 12:14:18

12 A I will restate that, if I may, in my own 12:14:21
13 language. 12:14:24

14 As I've stressed -- and I'll just make 12:14:25
15 this general observation, and this is not meant to 12:14:28
16 be antagonistic because I realize you have your job 12:14:31
17 to do, and I respect that. 12:14:35

18 The fact is that these are 12:14:38
19 oversimplifications. So, for example, if one takes 12:14:42
20 the specific example, not just of semaglutide, but 12:14:45
21 GLP-1 receptor agonists, I already alluded to the 12:14:49
22 concern about medullary carcinoma of the thyroid 12:14:52

1 because of the rat results. But that, even though 12:14:56
2 it's a concern in terms of safety, has not precluded 12:14:59
3 the administration of these agents. 12:15:04

4 And that is based on the assumption, A, 12:15:06
5 that maybe that's a unique phenomenon in these rats, 12:15:10
6 it's a species-specific effect; and further, there 12:15:14
7 has to be ongoing monitoring of individuals on these 12:15:19
8 class of agents to see whether this actually 12:15:22
9 develops. 12:15:24

10 I note that the same pharmaceutical 12:15:25
11 advertising not only talks about MEN2, but talks 12:15:28
12 about lumps in the thyroid. So there's clearly a 12:15:31
13 concern about this, but it has not precluded the 12:15:35
14 administration. 12:15:38

15 Let me go one step beyond that. There 12:15:39
16 are concerns about pancreatitis, which is 12:15:42
17 potentially a very problematic issue. And the 12:15:44
18 question is, well, this is some intrinsic feature of 12:15:47
19 GLP-1 agonists. There have been reports of 12:15:52
20 pancreatitis in individuals with type 2 diabetes 12:15:55
21 given various GLP-1 receptor agonists. 12:15:58

22 That, however, has not precluded their 12:16:01

1 continued administration, and because this is a 12:16:03
2 difficult situation in terms of how frequently does 12:16:06
3 that occur, is it really cause and effect due to the 12:16:08
4 GLP-1 receptor agonists. People with type 2 12:16:12
5 diabetes in general have an increased incidence of 12:16:15
6 pancreatitis. 12:16:17

7 So those are the issues that come to mind 12:16:18
8 when one talks about safety and tolerability. 12:16:21

9 And I will also say that the tolerability 12:16:24
10 question, this is where the issue of titration comes 12:16:27
11 in. It became apparent that to at least -- not 12:16:31
12 ensure, but to at least promote greater 12:16:41
13 tolerability, this kind of titration from lower 12:16:43
14 doses after a period of four weeks to a higher dose 12:16:46
15 and then a maintenance dose, that really was meant 12:16:49
16 to address tolerability. 12:16:52

17 So it's a real concern. 12:16:53

18 MR. REICH: I think we can go off the 12:16:58
19 record now. 12:17:00

20 (Recess from 12:17 p.m. until 12:41 p.m.) 12:40:58

21 BY MR. REICH: 12:40:58

22 Q Dr. Spiegel, you offered opinions here 12:41:02

1 that Dr. Goland's opinions on unexpected results 12:41:05
2 were not supported by relevant evidence. 12:41:08

3 Do you recall those? 12:41:10

4 A I do. 12:41:11

5 Q In your opinion, the evidence she cites 12:41:12
6 to, those were not relevant evidence because none of 12:41:17
7 the clinical trials compared semaglutide at 12:41:23
8 1.0 milligrams to liraglutide at 1.8 milligrams, 12:41:25
9 3.0 milligrams, or to semaglutide at 0.8 milligrams. 12:41:32

10 Is that fair? 12:41:36

11 MR. ANSTAETT: Objection to form. 12:41:37

12 A Those were some of the reasons, yes. 12:41:38

13 In general, the overarching things that 12:41:40
14 she really failed to consider, in my estimation, 12:41:43
15 prior art, among which were some of the things that 12:41:46
16 you just referred to. 12:41:50

17 Q What are the other reasons that you do 12:41:51
18 not think the SUSTAIN trials are relevant evidence 12:41:56
19 of unexpected results? 12:41:59

20 A Oh, one of the major objections there was 12:42:02
21 the lack of a comparison to the 1.8 milligram dose. 12:42:05
22 I think the head-to-head trial, if I'm recalling, 12:42:10

1 was SUSTAIN 10, I may have to go to the document, 12:42:14
2 but liraglutide 1.2 milligram versus semaglutide at 12:42:18
3 1.0, et cetera. 12:42:25

4 And the ostensible reason for limiting 12:42:27
5 the liraglutide dose to the 1.2 is, that was the 12:42:31
6 most commonly prescribed in Europe. 12:42:36

7 But if one looked carefully at other 12:42:41
8 papers, other trials, that was not the case in the 12:42:45
9 U.S. 1.8 milligram was purportedly the most 12:42:49
10 commonly prescribed in the U.S. So they failed to 12:42:55
11 compare. 12:42:55

12 And it's also very clear that there are 12:42:57
13 differences in efficacy going back to the issue of 12:43:00
14 degree of lowering of hemoglobin A1c. So that was a 12:43:02
15 key consideration. 12:43:05

16 The other thing was the NCT657 trial 12:43:05
17 where -- a phase 2 trial in which a variety of doses 12:43:10
18 of semaglutide were used, including 0.8 milligrams. 12:43:15
19 She did not compare to that prior art. 12:43:22

20 So those are two of the reasons. 12:43:28

21 Q So let's take those in turn. 12:43:30

22 You said they did not compare it to the 12:43:32

1 1.8 milligrams. Are you referring to the SUSTAIN 10
2 trial itself?

3 A Yes.

4 Q Okay. Are you aware of any head-to-head
5 study of semaglutide 1.0 against liraglutide at 1.8?

6 A I'm not.

7 Q So for Dr. Goland to come up with
8 relevant evidence, in your opinion, there would have
9 had to be a head-to-head study of 1.8 milligrams and
10 1.0 semaglutide?

11 MR. ANSTAETT: Objection to form.

12 A No, I don't think so. What I think is
13 that she could have cited -- and there are numerous
14 publications cited in my reply references -- trials
15 showing the undoubtedly greater efficacy of 1.8 to
16 1.2.

17 So if one is going to -- and it comes
18 back to the degree versus kind argument that we have
19 cited. The notion of unexpected results, degree
20 versus kind, if you want to make a fairer
21 comparison, compare it to the most effective -- more
22 effective dose of liraglutide.

1 And, in fact, there are publications 12:44:52
2 using as much as 3.0 milligrams of liraglutide. And 12:44:54
3 these are also cited in my response. And they are 12:44:59
4 very effective, including greater efficacy in terms 12:45:01
5 of weight loss. 12:45:04

6 So she basically seemed not to be either 12:45:05
7 aware or just didn't consult this relevant 12:45:09
8 literature. 12:45:14

9 Q You understand that the '462 patent is 12:45:16
10 for treating type 2 diabetes, correct? 12:45:19

11 A Absolutely. I understand that. 12:45:22

12 But that said, she emphasizes repeatedly 12:45:24
13 the weight loss phenomenon, which not only is not 12:45:28
14 relevant to '462 because it's for treating, just as 12:45:33
15 you just said, type 2 diabetes. Further, there is 12:45:36
16 the '003 patent which basically is a separate patent 12:45:38
17 for semaglutide explicitly for weight loss. 12:45:43

18 (Reporter interruption.) 12:45:53

19 Q So liraglutide at 3.0 milligrams, you 12:45:58
20 understand that is not indicated for type 2 12:46:01
21 diabetes, right? 12:46:05

22 A Understood. But the fact is that she was 12:46:06

1 emphasizing weight loss, and trying to make the 12:46:10
2 argument, at least my reading, that the -- first, 12:46:14
3 speciously, that the fact that semaglutide causes 12:46:20
4 substantial weight loss is somehow a unique feature 12:46:24
5 of that agent. And it's actually a class effect of 12:46:28
6 GLP-1 receptor agonists to varying degrees. We'll 12:46:35
7 come back to the efficacy argument, although this is 12:46:40
8 type 2 diabetes we're talking about, separate issue. 12:46:43

9 The notion that the weight loss is such a 12:46:45
10 unique feature of 1 milligram of semaglutide is not 12:46:47
11 supported by the data. 12:46:53

12 Q To your understanding, is 3.0 milligrams 12:46:56
13 of liraglutide indicated for type 2 diabetes? 12:47:00

14 A No. That's not the prescribing dose as 12:47:03
15 it was used, no. 12:47:08

16 Q Okay. And you -- 12:47:09

17 A For type 2 diabetes. 12:47:14

18 Q And you had referenced NCT657. 12:47:16

19 Do you recall that? 12:47:19

20 A Yes. 12:47:20

21 Q And you fault Dr. Goland for not 12:47:20
22 comparing 1.0 milligrams to the prior art 12:47:23

1	0.8 milligrams.	12:47:26
2	Did I understand that correctly?	12:47:27
3	A As you know, NCT657 used a whole range of	12:47:30
4	doses of semaglutide, one of which was 0.8, correct.	12:47:34
5	And she did not compare that at all.	12:47:40
6	Q To your understanding, as of the	12:47:45
7	invention date of the '462 patent, was there any	12:47:48
8	publicly available data on 0.8 milligrams of	12:47:52
9	semaglutide?	12:47:55
10	A Publicly available data in terms of	12:48:00
11	efficacy or -- what are you asking?	12:48:03
12	Q Any data. You tell me.	12:48:06
13	A Yeah, there was ClinicalTrials.gov which	12:48:10
14	specified the entire protocol.	12:48:15
15	Q Did it have any results?	12:48:18
16	A I've read about this argument before, and	12:48:22
17	let me just say that there were no results, as is	12:48:29
18	traditional, in ClinicalTrials.gov.	12:48:34
19	However, I am aware of -- and I have to	12:48:37
20	say right up front that I'm aware of this with	12:48:40
21	regard to the district court proceeding. So if I	12:48:43
22	can introduce that. I realize this is a separate	12:48:46

1 proceeding.

12:48:49

2 But there is a document, an SEC report
3 from Novo, which makes clear that they are about to
4 embark on phase 3 studies of semaglutide, and I
5 think this is circa 2009. So very clearly, that was
6 publicly available information indicating that they
7 were sufficiently impressed with the results of the
8 phase 2 trial as to embark on phase 3, which is an
9 expensive proposition.

12:48:50

12:48:54

12:48:58

12:49:02

12:49:07

12:49:09

12:49:11

12:49:15

10 Q Is that in your declaration?

12:49:16

11 A As I said, this is more relevant to the
12 district court. So not here.

12:49:19

12:49:21

13 Q And it's your understanding that in 2009,
14 Novo Nordisk told the world they were going to
15 proceed with phase 3 trials for semaglutide? Is
16 that what you said?

12:49:24

12:49:27

12:49:30

12:49:33

17 A I said --

12:49:34

18 MR. ANSTAETT: I'm sorry. Objection to
19 form.

12:49:34

12:49:35

20 But you can answer.

12:49:36

21 A What I said is that I am aware -- and let
22 me just say up front, while I've realized all along

12:49:36

12:49:40

1 that there's two parallel proceedings here, the IPR 12:49:44
2 which we're doing today and then a separate district 12:49:48
3 court, I necessarily have reviewed lots of material 12:49:52
4 relevant in both cases. 12:49:55

5 In most cases, the material I've reviewed 12:49:58
6 is stated and specified in my declarations for both. 12:50:01
7 This may be one instance where that's not the case. 12:50:06

8 Q But you do understand that there's no 12:50:11
9 publicly available data as to 0.8 milligrams 12:50:13
10 semaglutide as of the invention date. 12:50:17

11 Is that fair? 12:50:19

12 A What invention date -- sorry. 12:50:21

13 MR. ANSTAETT: Sorry. Objection to form. 12:50:23

14 But you can answer. 12:50:26

15 A What invention date are we talking about? 12:50:26
16 The invention date of the '462? 12:50:28

17 Q Yes. 12:50:31

18 A Not -- yes, you're correct, not in the 12:50:35
19 format of a published clinical trial result, for 12:50:39
20 example. 12:50:44

21 Q Was it available in any format? 12:50:44

22 A I keep alluding to the fact that there is 12:50:48

1 publicly available information in the SEC report 12:50:51

2 about their embarking on a phase 3 trial. 12:50:54

3 Q Are you aware that Novo Nordisk postponed 12:50:57

4 semaglutide entering phase 3 trials after this trial 12:51:01

5 was complete? 12:51:04

6 A Again, I may be introducing material from 12:51:07

7 parallel proceedings. 12:51:12

8 In Dr. Rosenstock's declaration, which I 12:51:13

9 reviewed, not Dr. Goland, Dr. Rosenstock, he dealt 12:51:16

10 explicitly with NCT657, and he made just the 12:51:20

11 objection that you're making now and tried to 12:51:25

12 postulate, A, that simply doing the phase 2 trial 12:51:27

13 doesn't presuppose the results will be positive, and 12:51:31

14 B, that there was supposedly a delay in launching 12:51:35

15 this trial, indicating that there might be reason to 12:51:39

16 think that phase 2 trial wasn't very effective. 12:51:42

17 However, I have contrary opinions about 12:51:44

18 that, and these are perhaps speculative opinions. 12:51:49

19 Before launching the phase 3 trial, they may have 12:51:55

20 been concerned about scale-up in manufacturing to be 12:51:58

21 able to generate sufficient semaglutide, even to 12:52:01

22 conduct the trial, much less to market it 12:52:04

1 eventually.

12:52:06

2 Second, liraglutide, their own agent, was
3 available, approved, and being marketed, and some
4 consideration, I'm sure, about maximizing -- and by
5 the way, specified in this report, in the IPR
6 report, one of our references is an SEC report --
7 excuse me, not SEC -- a financial report from Novo
8 which says that roughly in 2010, that may be the
9 year, the market share for liraglutide in the U.S.
10 may have been as high as 48 percent.

12:52:06

12:52:11

12:52:17

12:52:21

12:52:24

12:52:28

12:52:33

12:52:41

12:52:46

11 So I don't think one can conclude much
12 from delaying embarking on the phase 3. There may
13 have been a number of reasons for that having
14 nothing to do with a lack of encouraging results in
15 NCT657.

12:52:48

12:52:52

12:52:56

12:52:58

12:53:02

16 Q On your materials considered list, do you
17 note Dr. Rosenstock's declaration?

12:53:08

12:53:11

18 A No. As I said, this is part of the
19 parallel proceedings thing. So I was given lots of
20 material to review, and, you know, I'm voracious in
21 reviewing these things. And so that's what I did.

12:53:16

12:53:19

12:53:22

12:53:25

22 Q But if I understand your opinion, you

12:53:28

1	think that Novo Nordisk, rational actor, delayed	12:53:30
2	semaglutide entering phase 3 trials despite its	12:53:36
3	promising results because of liraglutide?	12:53:40
4	(Cross-talk.)	12:53:47
5	MR. ANSTAETT: I just want to make sure	12:53:47
6	my objection -- I interrupted Josh. So just	12:53:49
7	objection to form.	12:53:52
8	But you can answer.	12:53:53
9	A Anything I said with regard to the	12:53:55
10	reasons for their delay would, by definition, be	12:53:59
11	speculative since I'm not privy to their management	12:54:02
12	and their considerations in terms of how to proceed.	12:54:06
13	So there could be any number of reasons.	12:54:09
14	I specified two, the overlap with	12:54:12
15	liraglutide marketing, the issue of scale-up in	12:54:14
16	terms of manufacture, which clearly has become an	12:54:18
17	issue. This is the reason you have all these	12:54:21
18	compounding pharmacies substituting their	12:54:25
19	semaglutide for the Novo Nordisk product because	12:54:29
20	Novo Nordisk must list shortage, which then gives	12:54:33
21	these compounding pharmacies from the FDA rights to	12:54:36
22	compound and market that agent.	12:54:40

1 So again, but these are purely 12:54:42

2 speculative arguments on my part. 12:54:44

3 Q Semaglutide is so successful that Novo 12:54:50

4 Nordisk can't even supply the consumer demand for 12:54:54

5 it? Is that what I heard you say? 12:54:59

6 MR. ANSTAETT: Objection to form. 12:55:01

7 A First of all, commercial success is not 12:55:02

8 one of the secondary considerations that Dr. Goland 12:55:05

9 addressed. So we would exclude that with regard to 12:55:09

10 this proceeding. 12:55:13

11 Second of all, if you're asking me about 12:55:14

12 commercial success, yes, undoubtedly. But my belief 12:55:19

13 would be that that commercial success has very 12:55:23

14 little to do with treatment of type 2 diabetes, the 12:55:25

15 subject of the '462 patent, and everything to do 12:55:28

16 with weight loss. And not only weight loss but 12:55:31

17 weight loss for cosmetic reasons as opposed to 12:55:35

18 health reasons. 12:55:38

19 Q And what's your understanding for that -- 12:55:39

20 let me withdraw that. 12:55:44

21 What is the basis for your belief that 12:55:46

22 the commercial success of Ozempic has very little to 12:55:49

1 do with treatment of type 2 diabetes and everything 12:55:52
2 to do with weight loss, and not only weight loss but 12:55:54
3 weight loss for cosmetic reasons? 12:55:59

4 A It has to do with material that 12:56:01
5 Dr. Goland herself cited as examples of praise. She 12:56:07
6 cited an article in The New Yorker by a physician, 12:56:11
7 Dhruv Khullar, and if one read that, it was all 12:56:15
8 about the weight loss, not about treatment of type 2 12:56:18
9 diabetes. Mentioned once maybe at the beginning, 12:56:21
10 but ultimately, that was where it was happening. 12:56:23

11 The New York Times article she cited, 12:56:26
12 which really talked about treatment of other 12:56:30
13 diseases, not specifically type 2 diabetes. But 12:56:32
14 again, we, in this proceeding, provided an 12:56:35
15 alternative New York Times piece, it's actually 12:56:40
16 their ethics column, and just making it very clear 12:56:44
17 that -- abundantly clear that the issue of taking 12:56:48
18 Ozempic for cosmetic purposes in terms of weight 12:56:51
19 loss. 12:56:54

20 And this is, again, not something that I 12:56:54
21 can quantitate. I'll say that up front. But the 12:56:58
22 media, both print media and -- Oprah Winfrey had a 12:57:03

1	nationally televised program really all on this	12:57:11
2	subject.	12:57:15
3	Q Have you done any analysis of what number	12:57:17
4	of prescriptions of Ozempic are for patients with	12:57:20
5	type 2 diabetes?	12:57:24
6	A I have not.	12:57:27
7	Q And you've referred to a New York Times	12:57:28
8	article. If you could turn to page 109 of your	12:57:31
9	report, paragraph 306. Let me know when you're	12:57:33
10	there.	12:57:49
11	A Yes, I have it.	12:57:49
12	Q Are you referring to Exhibit 1117 as the	12:57:50
13	basis for your opinion on this -- the basis that it	12:57:53
14	was made abundantly clear that the issue of taking	12:58:03
15	Ozempic for cosmetic purposes?	12:58:06
16	A I am referring to 1117, but that is only	12:58:09
17	one of numerous, numerous articles I could cite.	12:58:13
18	Numerous.	12:58:17
19	For example, the State of North Carolina	12:58:18
20	has withdrawn state support for its employees for	12:58:22
21	Ozempic prescriptions. And the rationale was that	12:58:26
22	it was being overused massively, in their	12:58:31

1 estimation, not my value judgment, and economically 12:58:35
2 would be very, very injurious to the state 12:58:39
3 government. That's one point that I would make. 12:58:41

4 Another point I would make -- I've 12:58:45
5 already referred to the compounding pharmacies and 12:58:47
6 their provision of Ozempic. But let me also point 12:58:50
7 out that various telehealth companies have gotten 12:58:56
8 into this market, and are marketing to patients 12:58:59
9 Ozempic without ever examining the patient, without 12:59:04
10 ever taking into consideration whether they have 12:59:08
11 type 2 diabetes at all. This is the same -- 12:59:12

12 (Cross-talk.) 12:59:16

13 A Go ahead, I'm sorry. 12:59:17

14 Q Do you discuss that anywhere in your 12:59:19
15 declaration? 12:59:21

16 A I was giving one example of many possible 12:59:24
17 ones that could be given. 12:59:28

18 Q And let's -- 12:59:30

19 (Cross-talk.) 12:59:31

20 A They were not explicitly cited in the 12:59:33
21 document, correct. 12:59:35

22 Q They're not mentioned, right? You didn't 12:59:39

1 mention the North Carolina insurance regime at all 12:59:42

2 in here, did you, yes or no? 12:59:44

3 A No. 12:59:46

4 MR. REICH: If we could pull up -- 12:59:47

5 actually, hold on. 12:59:49

6 Q Do you think Exhibit 1117 is credible 12:59:53

7 support for your opinion that this is widespread use 12:59:57

8 of using Ozempic for off-label weight loss? 13:00:00

9 MR. ANSTAETT: Objection to form. 13:00:08

10 A I think it's one anecdotal exhibit. It 13:00:09

11 does not quantitate, nor does it allow one to 13:00:12

12 quantitate how prevalent, how widespread this is. 13:00:16

13 But there have been, as I've suggested, 13:00:20

14 numerous, numerous reports along these lines. And 13:00:22

15 that's the basis of my opinion. I was just using 13:00:26

16 this as one credible example. 13:00:29

17 Q So you think this is a credible example, 13:00:33

18 though, right? 13:00:35

19 A Absolutely. 13:00:36

20 MR. REICH: If we could pull up 13:00:38

21 Exhibit 1117, please, Kollin. 13:00:39

22 (Previously marked Exhibit 1117 presented 13:00:39

1	to the witness.)	13:00:39
2	MR. REICH: And Dave, if you want to hand	13:00:44
3	him a paper copy, that's fine with me.	13:00:45
4	MR. ANSTAETT: Yeah, I think we have it.	13:00:47
5	THE WITNESS: This is 1118.	13:01:21
6	MR. ANSTAETT: Just give us one second,	13:01:21
7	Josh. We're looking for the paper.	13:01:21
8	MR. REICH: No worries.	13:01:21
9	MR. ANSTAETT: It looks like we may have	13:01:21
10	the wrong document in the folder, so we may not have	13:01:23
11	a paper copy of 1117. So maybe if we put it up and	13:01:23
12	then also put it in the chat.	13:01:26
13	(A discussion was held off the record.)	12:38:40
14	BY MR. REICH:	13:02:06
15	Q Dr. Spiegel, this is Exhibit 1117 that	13:02:06
16	you cite as support for your opinion on this	13:02:08
17	widespread off-label use of Ozempic, right?	13:02:12
18	MR. ANSTAETT: Josh, can you hang on for	13:02:16
19	just one second? I'm sorry. It's in the chat. I	13:02:19
20	just need to download it.	13:02:22
21	Okay, I've got it. Thank you.	13:02:49
22	Q Do you need the question again,	13:02:54

1	Dr. Spiegel?	13:02:56
2	A Yes, please.	13:02:56
3	Q So this is Exhibit 1117 that you cite as	13:02:58
4	support for your opinion of this widespread	13:03:03
5	off-label use of Ozempic, correct?	13:03:07
6	A I want to qualify that. I cite this as	13:03:10
7	one concrete but anecdotal example. And you'll note	13:03:16
8	that in the text here, the -- join the masses taking	13:03:21
9	semaglutide for weight loss. That's what it says in	13:03:28
10	the first sentence.	13:03:31
11	Now, that doesn't mean that this person	13:03:31
12	has access to some rigorous quantitation of what --	13:03:34
13	how many people comprise masses and what they're	13:03:40
14	taking it for.	13:03:43
15	With that said, even though this is the	13:03:43
16	only example that I listed within this declaration,	13:03:47
17	I necessarily am reading constantly, and like any	13:03:52
18	other sentient human being, I've been exposed to not	13:03:57
19	only a variety of public media and other potentially	13:04:02
20	anecdotal sources of information on this topic, but	13:04:07
21	also my colleagues in practice.	13:04:11
22	Dr. Sriram Machineni who heads our	13:04:14

1 obesity treatment center at Einstein Montefiore is 13:04:20
2 an important source of information on this subject, 13:04:23
3 and I can gauge how prevalent this is, at least an 13:04:25
4 approximation, from what he informs me. 13:04:29

5 So that would be my response. Yes, this 13:04:32
6 is a single anecdotal example, and that is as far as 13:04:34
7 I would go with it. 13:04:38

8 Q I'm trying really good here. I 13:04:39
9 appreciate that we're almost done, but I asked if 13:04:44
10 you cited this, and there was a bunch of that that 13:04:47
11 wasn't responsive. So to get through the day, if 13:04:49
12 you could just try and answer my question, and then 13:04:52
13 your counsel is free to ask questions after this. 13:04:54
14 But just to move it along, all right. 13:04:56

15 A Yes, I cited those. 13:04:59

16 Q Okay. And it's written by name withheld. 13:05:01

17 Do you see that? 13:05:06

18 A I do. 13:05:06

19 Q And you take this as a credible source 13:05:07
20 that there are masses of people that are taking 13:05:12
21 Ozempic off-label. 13:05:15

22 Is that correct? 13:05:17

1	A	It is correct, for the following reason.	13:05:19
2		You're imputing to name withheld some bogus or I'm	13:05:21
3		guessing sinister or some other lack of validity,	13:05:28
4		lack of face validity.	13:05:32
5		I would argue -- and I read this column	13:05:34
6		frequently, as I do the diagnostic column that	13:05:37
7		appears in The Sunday Times Magazine.	13:05:41
8		This individual has friends, and he's	13:05:43
9		asking about criticizing these friends. And so if	13:05:46
10		he put his name there, he'd be doxing himself and	13:05:50
11		unmasking himself. That's the reason name withheld.	13:05:55
12		And like the rest of the United States,	13:05:58
13		one would have to be totally oblivious to a mass of	13:06:00
14		information which, while not quantitative, indicates	13:06:05
15		that this is indeed a widespread phenomenon; this	13:06:08
16		being people taking semaglutide for weight loss and	13:06:13
17		in some instances -- and I wouldn't quantify this --	13:06:17
18		he says here, neither of whom is obese. So this is	13:06:20
19		even more peculiar. But lots of obese people	13:06:24
20		without type 2 diabetes might be taking it. And	13:06:27
21		that's my point.	13:06:32
22	Q	I think you said I'm imputing to name	13:06:35

1 withheld some bogus or I'm guessing some sinister or 13:06:38

2 other lack of validity. 13:06:42

3 Is it fair to say that you're imputing 13:06:43

4 that this person has firsthand knowledge of the 13:06:45

5 amount of people in the world taking Ozempic 13:06:48

6 off-label for weight loss? 13:06:51

7 MR. ANSTAETT: Objection to form. 13:06:54

8 A And I would wonder how you would define 13:06:55

9 "firsthand." Necessarily, this individual, being a 13:06:58

10 member of the public, is exposed to all the 13:07:03

11 information that we are constantly exposed to about 13:07:07

12 the popularity and prevalence of this drug and the 13:07:10

13 ways that it's marketed. 13:07:14

14 And so that does not constitute rigorous 13:07:15

15 knowledge of an exact quantitation of numbers of 13:07:20

16 individuals, but it does constitute evidence that 13:07:23

17 this is a prevalent practice. 13:07:25

18 MR. REICH: We can take this down. 13:07:30

19 Q But I think we can agree, at least, that 13:07:31

20 it doesn't require an expert to read that editorial 13:07:35

21 and draw whatever conclusions one might want. 13:07:38

22 Is that fair? 13:07:41

1	MR. ANSTAETT: Objection to form.	13:07:42
2	You can answer.	13:07:43
3	A Yes. What I would say is, you're taking	13:07:43
4	this out of context. And that needs to be added to	13:07:46
5	the record.	13:07:50
6	The reason I say you're taking it out of	13:07:51
7	context is that we're talking about my reply to	13:07:54
8	Dr. Goland's declaration.	13:07:56
9	Dr. Goland is taking a New York Times	13:07:58
10	article similarly out thin air, so to speak, and	13:08:02
11	citing it as an example of great praise for Ozempic.	13:08:09
12	Praise for Ozempic for what? For treatment of	13:08:14
13	type 2 diabetes? Absolutely not.	13:08:16
14	And so this was just a counter example	13:08:18
15	showing something in The New York Times, the same	13:08:22
16	august newspaper, basically making it clear that	13:08:25
17	there's lots of Ozempic use, "lots" being a	13:08:29
18	nonquantitative term, for weight loss as opposed to	13:08:32
19	the treatment of type 2 diabetes.	13:08:36
20	Q The article that you're referring to that	13:08:38
21	Dr. Goland cited was written by a doctor, right?	13:08:41
22	A No. The article that was written by a	13:08:44

1 doctor is in The New Yorker article. And I'd have 13:08:47
2 to check the author of The New York Times article 13:08:51
3 that she cited. 13:08:54

4 The author of -- Dhruv Khullar, I'm 13:08:56
5 familiar with him. He's actually at one of the 13:09:00
6 local hospitals, health systems. And he very 13:09:02
7 quickly deviated, as I said, from discussions. 13:09:08
8 She's citing this in support of praise of Ozempic in 13:09:12
9 relation to the '462 patent. But the article was 13:09:16
10 all about weight loss. It was not about in 13:09:18
11 particular treatment of type 2 diabetes. 13:09:22

12 Q So The New York Times article -- 13:09:24
13 (Cross-talk.) 13:09:29

14 A The New York Times article's major 13:09:29
15 focus -- 13:09:32

16 Q I'm sorry. 13:09:32

17 The New York Times article quotes from 13:09:34
18 doctors, correct, and provides names of those 13:09:37
19 doctors that are providing their opinion? 13:09:39

20 Do you recall that? 13:09:43

21 A I'm recalling a quote from a mass general 13:09:45
22 female physician who says, I would not call it a 13:09:48

1 game changer, referring to Ozempic, it's just a tool
2 in our toolbox.

3 And I'm aware that Dr. Goland took issue
4 with that. She does call it a game changer.

5 Q Okay. I don't think you answered my
6 question.

7 The New York Times article has quotes
8 that are attributable to doctors that are named in
9 The New York Times article.

10 Do you recall that?

11 A I recall that. But the relevant point
12 here is that they're not providing praise for
13 Ozempic as a treatment for type 2 diabetes.

14 Q So earlier we had been discussing
15 0.8 milligrams of semaglutide in NCT657.

16 Do you recall that?

17 A I do.

18 Q Is it your understanding that for
19 unexpected results, you measure that based on the
20 expectation of a person of skill as of the time of
21 the invention?

22 MR. ANSTAETT: Objection to form.

1 A I think that's a fair definition, at 13:10:47
2 least to my understanding. 13:10:49

3 Q If you have no data on 0.8 milligrams as 13:10:50
4 of the invention date, how, in your opinion, would a 13:10:56
5 person of skill have an expectation how 13:11:02
6 1.0 milligrams would behave based on that? 13:11:07

7 A That NCT657 was cited as just one example 13:11:14
8 of prior art. 13:11:19

9 As I've indicated, there are other 13:11:20
10 examples of prior art which undercut Dr. Goland's 13:11:23
11 assertion. And in one of the references that we 13:11:26
12 cited, there's an explicit reference to the fact 13:11:31
13 that the greater efficacy of semaglutide compared to 13:11:35
14 liraglutide, for example, could be due, and I'm 13:11:39
15 quoting now, to minor changes in structure. And 13:11:42
16 indeed, they are minor. There are two changes in 13:11:45
17 structure between those two GLP-1 analogs. 13:11:48

18 So the totality of the evidence which she 13:11:55
19 failed to compare the '462 patent to in terms of 13:11:57
20 prior art suggests that she is not entitled to draw 13:12:03
21 conclusions about unexpected results. 13:12:07

22 In fact, one might say that they were 13:12:11

1 potentially predictable. 13:12:14

2 Q Okay. Just go back to my original 13:12:17
3 question. 13:12:20

4 I asked, how would a person of skill 13:12:20
5 expect 1.0 milligrams to behave based on 13:12:24
6 0.8 milligrams of semaglutide if there were no data 13:12:30
7 as of the time of the invention? 13:12:33

8 MR. ANSTAETT: Objection to form. 13:12:36

9 A The person would not be relying solely on 13:12:40
10 NCT657. That could be one component, the fact that 13:12:46
11 it advanced through a phase 2 trial and that the 13:12:49
12 doses used which are cited in that study are 13:12:52
13 available. 13:12:55

14 But as I've already indicated, there are 13:12:56
15 other reasons to doubt the secondary consideration 13:12:59
16 of unexpected results that go beyond the NCT657 13:13:04
17 trial. And I've already cited several examples of 13:13:07
18 that, including a comparison to liraglutide. 13:13:10

19 And as I've said all along, there really 13:13:14
20 is a spectrum of results in the history of 13:13:17
21 development of these GLP-1 receptor agonists. 13:13:20

22 So it's not as if semaglutide emerged 13:13:22

1 suddenly as this extraordinary unique compound with 13:13:25

2 differences in kind as opposed to degree. 13:13:29

3 Q Dr. Spiegel, you fault Dr. Goland for not 13:13:32

4 comparing 1.0 milligrams of semaglutide -- the 13:13:34

5 results from 1.0 milligrams of semaglutide to 13:13:37

6 0.8 milligrams. 13:13:41

7 Is that correct? 13:13:42

8 A I do fault her for not including 13:13:44

9 consideration of the NCT657 results, yes. 13:13:47

10 Q How, in your opinion, was she supposed to 13:13:51

11 compare the expectations or, you know -- let me 13:13:55

12 withdraw that. 13:14:00

13 As of the invention date, how would a 13:14:00

14 POSITA have expected 1.0 milligrams of semaglutide 13:14:05

15 to behave based on 0.8 milligrams of semaglutide if 13:14:08

16 there were no results available? 13:14:12

17 MR. ANSTAETT: Objection to form. 13:14:15

18 A Let me just say that we have Dr. Goland 13:14:19

19 giving her declaration in real time now as opposed 13:14:28

20 to the time frame that you're discussing. So in 13:14:33

21 that sense, what we -- the relevance of the 13:14:36

22 0.8 milligram dose in NCT657 is that if one goes 13:14:42

1 beyond the immediate time frame, 2008, 2009, when
2 that was publicly available, but before the '462
3 patent, one already would have predicted that the
4 1 milligram dose would be efficacious.

5 Q So in your opinion, the proper comparison
6 should have been the results from 1.0 milligrams
7 semaglutide to the results of 0.8 milligrams
8 semaglutide despite the fact that there were no
9 results for 0.8 milligrams semaglutide in the art as
10 of the invention date?

11 MR. ANSTAETT: Objection to form.

12 A No. What I'm stressing, in fact, is that
13 the most compelling omission on Dr. Goland's part
14 with regard to the secondary considerations of
15 unexpected results in particular is the comparison
16 to liraglutide and semaglutide, in which there are a
17 mere two amino acid differences -- one amino acid
18 difference and one difference in the fatty acid
19 chain attachment. And those differences are very
20 limited.

21 And given the effectiveness of
22 liraglutide and the prediction based on those

1 differences, which engender resistance to DPP-4 13:16:15
2 degradation at position 8, substituting 13:16:22
3 alpha-aminobutyrate instead of the native alanine, 13:16:28
4 and the attachment of a diacyl chain at lysine 26 as 13:16:30
5 opposed to a single acyl chain in liraglutide, would 13:16:34
6 be predicted by a person of ordinary skill in the 13:16:39
7 art to prolong the half-life considerably, allowing 13:16:42
8 the transition from one-per-day dose to one-per-week 13:16:48
9 dose, and overall, giving greater effectiveness. 13:16:54

10 That is the comparison she failed to 13:16:57
11 make. It's a comparison that I've already said, we 13:17:00
12 quoted, is cited one of the clinical trials and is 13:17:03
13 stated very clearly. These minor changes would be 13:17:06
14 predicted to give greater clinical utility. 13:17:10

15 Q In your opinion, there's only two minor 13:17:16
16 differences between liraglutide and semaglutide? 13:17:18

17 A I'm quoting the investigators in that 13:17:22
18 particular study. And that quote is in the reply. 13:17:27
19 They are the ones who characterized them as minor. 13:17:30
20 And again, that's a matter of what you consider 13:17:33
21 minor. 13:17:38

22 Q But it's your understanding that there 13:17:41

1 are only two differences between liraglutide and 13:17:42
2 semaglutide? 13:17:44

3 A Structures, if one looks at a 13:17:47
4 head-to-head comparison, involve an 13:17:51
5 alpha-aminobutyrate at position 8 starting from 7 to 13:17:54
6 37 for native GLP-1 instead of the alanine. So 13:17:59
7 alpha-aminobutyrate in semaglutide versus alanine in 13:18:05
8 liraglutide and GLP-1, a critical residue because of 13:18:10
9 the determination of DPP-4 degradation 13:18:13
10 susceptibility. 13:18:17

11 And by the way, that prior art was known 13:18:18
12 even in 1990s. Novo Nordisk and other companies had 13:18:21
13 already shown what constitutes the active site and 13:18:27
14 the importance of that alanine residue. So that was 13:18:30
15 clearly known. 13:18:34

16 Second of all, the other change, both of 13:18:35
17 them have a change at a lysine in position 34 where 13:18:39
18 an arginine is substituted, and the reason -- so 13:18:45
19 they are the same there. 13:18:48

20 But the reason for that substitution is 13:18:49
21 the derivatization of lysine 26 in the case of 13:18:51
22 liraglutide by a glutamic acid and a single acyl 13:18:57

1 chain, that being a fatty acid chain which promotes 13:19:02
2 albumin binding. And instead, in semaglutide, a 13:19:06
3 spacer -- and I don't know actually the exact 13:19:10
4 chemical structure of that spacer or even if it's 13:19:14
5 been specified -- but now a diacyl chain, two fatty 13:19:16
6 acids. 13:19:20

7 So the inference is that you would have 13:19:21
8 greater albumin binding and prolongation power. 13:19:22

9 (Reporter interruption.) 13:19:22

10 A Albumin binding and, therefore, a greater 13:19:34
11 half-life, longer half-life. 13:19:37

12 Q Dr. Spiegel, do you know if liraglutide 13:19:43
13 is resistant to DPP-4 cleavage? 13:19:45

14 A A prediction based on having the native 13:19:53
15 alanine would be that if you only had the peptide, 13:19:57
16 it might well be non-resistant. But the crucial 13:20:03
17 thing is that the albumin binding means that the 13:20:07
18 bulk of the peptide is circulating in an 13:20:10
19 albumin-bound form not available for DPP-4 13:20:14
20 degradation. 13:20:18

21 That's my understanding. 13:20:19

22 Q You don't dispute that Dr. Goland 13:20:20

1 compares liraglutide to semaglutide, correct?

13:20:27

2 A She compares it most explicitly -- and
3 again, I hope I have the correct number here -- in
4 the SUSTAIN 10 trial, which was the head-to-head
5 comparison. It was only, as we've belabored, to the
6 1.2 milligram dose, not the more efficacious
7 1.8 milligram does, which clearly has been used in
8 other trials and for treatment of type 2 diabetes.

13:20:30

13:20:34

13:20:36

13:20:40

13:20:45

13:20:50

13:20:52

9 Q I'm going to try again with some yes,
10 nos, maybe.

13:20:53

13:20:57

11 You agree that Dr. Goland compared
12 semaglutide to liraglutide, yes or no?

13:20:58

13:21:02

13 MR. ANSTAETT: Objection, form, asked and
14 answered.

13:21:05

13:21:07

15 He can answer however he likes.

13:21:07

16 A I will answer, and I will state that I
17 will only answer a yes if you specify compares it to
18 1.2 milligrams liraglutide. Then I would say yes.
19 If you don't say that, then she -- I would say she
20 did not make a fair comparison.

13:21:09

13:21:12

13:21:17

13:21:20

13:21:24

21 Q And the SUSTAIN 10 clinical trial
22 compared 1.2 milligrams of liraglutide to

13:21:26

13:21:29

1	1.0 milligrams of semaglutide, correct?	13:21:34
2	A Let me ask my colleague here to give me	13:21:37
3	the reference, because we keep referring to	13:21:41
4	SUSTAIN 10, so I want to actually look at the	13:21:44
5	SUSTAIN 10 trial.	13:21:46
6	Q I'll tell him not to. You can answer my	13:21:47
7	question to the best of your recollection, and then	13:21:49
8	we can move on.	13:21:51
9	A Yes, to the best of my recollection.	13:21:52
10	Q And earlier you had testified that you're	13:21:58
11	not aware of any head-to-head trial between	13:22:00
12	1.8 milligrams liraglutide and 1.0 milligrams	13:22:06
13	semaglutide.	13:22:09
14	Is that correct?	13:22:09
15	A That is correct.	13:22:09
16	Q You don't provide any opinions that	13:22:15
17	liraglutide at 1.8 milligrams is comparable to the	13:22:18
18	efficacy of semaglutide at 1.0 milligrams, correct?	13:22:21
19	MR. ANSTAETT: Objection to form.	13:22:25
20	A I would say yes.	13:22:27
21	Q You don't dispute that Dr. Goland	13:22:38
22	compared the results of 1.0 milligrams semaglutide	13:22:41

1 to the art that was available based on the clinical 13:22:45

2 studies that were available to her? 13:22:50

3 MR. ANSTAETT: Objection to form. 13:22:52

4 A I would say that she cited the various 13:22:55

5 SUSTAIN trials, several of which involve GLP-1 13:23:00

6 receptor agonists, including dulaglutide, for 13:23:05

7 example, so not just liraglutide. 13:23:11

8 But she confined herself also to 13:23:12

9 FDA-approved drugs as opposed to drugs that were 13:23:15

10 still not FDA approved. 13:23:21

11 So there may well have been relevant 13:23:24

12 prior art which she did not compare to. 13:23:27

13 Q Did you identify any of that prior art 13:23:33

14 that she should have compared semaglutide 13:23:35

15 1.0 milligrams to in your declaration? 13:23:38

16 MR. ANSTAETT: Objection, form. 13:23:41

17 A Yes. That gets us back to the NCT657 13:23:42

18 issue where you have the semaglutide and our 13:23:46

19 discussion about whether there were results 13:23:51

20 available from the 0.8 milligram dose. 13:23:54

21 Q Other than NCT657, is there any prior art 13:23:57

22 that you think Dr. Goland should have compared to 13:24:00

1 the 1.0 milligrams semaglutide dose? 13:24:02

2 MR. ANSTAETT: Objection to form. 13:24:04

3 A More generally -- let me say, yes, in the 13:24:08
4 following sense. We're -- again, your question is 13:24:12
5 taking this out of context. The discussion should 13:24:16
6 be focused on her arguments and evidence in favor of 13:24:19
7 the secondary considerations, unexpected results, 13:24:25
8 satisfying a long-felt unmet need. 13:24:33

9 And in her comparison, by and large, she 13:24:36
10 did not compare to the relevant prior art. And 13:24:39
11 again, my argument is that we're talking about a 13:24:43
12 difference in degree, not kind. 13:24:48

13 So irrespective -- even if we were to 13:24:52
14 grant, as I might, that if there were a head-to-head 13:24:57
15 comparison between 1.0 milligrams semaglutide and 13:25:01
16 1.8 milligram liraglutide, the 1.0 might still be 13:25:04
17 somewhat better. 13:25:07

18 But that, to me, is not a basis for a 13:25:08
19 secondary consideration conclusion with regard to 13:25:11
20 satisfying a long-felt unmet need, nor the 13:25:13
21 unexpected results. And that's simply because, 13:25:18
22 while there may be some slightly greater efficacy, 13:25:22

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1	it is a matter of degree, not kind.	13:25:25
2	Q I'm just trying to figure out -- you keep	13:25:39
3	saying she didn't compare it to the relevant prior	13:25:41
4	art, right?	13:25:44
5	A Yes.	13:25:44
6	Q And you identify at 0.8 milligrams as one	13:25:45
7	of the things that, in your opinion, Dr. Goland	13:25:48
8	should have compared it to.	13:25:50
9	Fair?	13:25:52
10	A Yes.	13:25:52
11	Q And another one is 1.8 milligrams of	13:25:53
12	liraglutide, you think she should have compared	13:25:57
13	1.0 milligrams of semaglutide to, correct?	13:26:00
14	A Yes. But --	13:26:02
15	Q Is there anything else that you	13:26:05
16	identified in your declaration that, in your	13:26:08
17	opinion, Dr. Goland should have compared	13:26:12
18	1.0 milligrams of semaglutide to?	13:26:14
19	A No. But back to the 1.8 milligrams	13:26:19
20	liraglutide, there does not need to be a	13:26:24
21	head-to-head comparison for her to refer to that as	13:26:27
22	prior art. If there is credible significant	13:26:31

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1 clinical testing and evidence at that dose showing a 13:26:35
2 certain degree of efficacy, one can extrapolate. 13:26:39

3 And in fact, let me just say that there 13:26:42
4 are publications cited, I think Madsbad may be one 13:26:45
5 and others, which do analyses across the class of 13:26:49
6 GLP-1 receptor agonists. 13:26:56

7 And they bolster and underscore the point 13:26:58
8 that I've been making all along, that there is a 13:27:01
9 spectrum; that undoubtedly semaglutide is high on 13:27:04
10 that spectrum with regard to efficacy and lowering 13:27:09
11 A1c, but that there is a lot of prior art, other 13:27:12
12 GLP-1 receptor agonists, of which liraglutide is 13:27:19
13 one, that are quite efficacious. 13:27:22

14 And hence, conclusions with regard to 13:27:25
15 satisfying a long-felt unmet need and unexpected 13:27:28
16 results, in my opinion, just my opinion, are not 13:27:32
17 warranted. 13:27:35

18 Q In your opinion, it's okay to compare 13:27:45
19 results across clinical trials? 13:27:47

20 MR. ANSTAETT: Objection to form. 13:27:50

21 You can answer. 13:27:51

22 A Yes. That's known as a meta-analysis. 13:27:51

1 And a meta-analysis has very rigorous considerations 13:27:55
2 of how you stack these clinical trials. There need 13:27:58
3 to be rigorous criteria with regard to the patient 13:28:04
4 populations. 13:28:06

5 For example, you would not be permitted 13:28:07
6 to compare two clinical trials which are looking in 13:28:09
7 one case only at females with type 2 diabetes and 13:28:13
8 the other case only at males with type 2 diabetes 13:28:16
9 because they might have very different results. 13:28:21
10 There may be a gender-specific difference. 13:28:23

11 So if there is a rigorously applied 13:28:25
12 meta-analysis, of which there are some for GLP-1 13:28:29
13 receptor analogs, and some of these are included in 13:28:32
14 our material, yes, it is quite fair. And that is 13:28:35
15 done on an ongoing basis. There's a whole group 13:28:38
16 called the Cochrane Group in the UK that does that 13:28:42
17 all the time. 13:28:45

18 Q If you can turn to page 86, paragraph 243 13:28:47
19 of your declaration, please. 13:28:51

20 A Okay. 13:29:05

21 Q You wrote that SUSTAIN 10 merely 13:29:05
22 validates the prediction a POSA would have made 13:29:08

1	based on the prior art, namely, that developing a	13:29:11
2	longer acting GLP-1 analog could be more effective	13:29:14
3	in terms of treating diabetes, in certain doses.	13:29:18
4	Do you see that?	13:29:22
5	A I do.	13:29:22
6	Q How do you know which doses will be more	13:29:23
7	effective?	13:29:28
8	MR. ANSTAETT: Objection to form.	13:29:31
9	A Could you clarify which doses of what?	13:29:33
10	Q You wrote, in certain doses, the longer	13:29:36
11	acting GLP-1 analog could be more effective.	13:29:40
12	Did you write that?	13:29:43
13	A Yes.	13:29:44
14	Q How do you know which doses those certain	13:29:46
15	doses are?	13:29:50
16	A The sense of what's written here is that	13:29:57
17	one will be extrapolating from other information	13:30:24
18	developed, A, about previously developed GLP-1	13:30:32
19	analogs, and one could predict that if you made	13:30:36
20	structural changes of the kind that we described in	13:30:45
21	semaglutide so that it would be longer acting, that	13:30:47
22	it would be more effective.	13:30:51

1 And as far as the specific doses, one 13:30:53
2 would really have to look at the liraglutide doses, 13:30:57
3 and those doses are specified. Those were known. 13:31:06
4 Those were available to Dr. Goland, or would be 13:31:10
5 available to a POSA. 13:31:13

6 And then if you now say that superimposed 13:31:17
7 on liraglutide, you've made changes which are going 13:31:19
8 to make this new GLP-1 analog longer acting, A, it 13:31:22
9 would be more effective, and the doses would be in 13:31:27
10 the same order of magnitude, in the same range as 13:31:31
11 the liraglutide doses. And indeed, they are. 13:31:35

12 So, for example, she compared in 13:31:39
13 SUSTAIN 10 to the 1.2 milligrams dose. I've made 13:31:42
14 the argument throughout -- I mean, here it does say 13:31:47
15 3 milligrams, but 1.8 is the other thing that I've 13:31:50
16 referred to. 13:31:55

17 And these are in the same ballpark, the 13:31:55
18 same order of magnitude as what eventually becomes 13:31:58
19 semaglutide doses that are in the prescribing 13:32:06
20 indication for Ozempic. 13:32:09

21 Q So in your opinion, you look to prior 13:32:16
22 GLP-1 analogs, and that dosing informs the brand-new 13:32:19

1	structure of semaglutide?	13:32:24
2	A Depends how --	13:32:26
3	MR. ANSTAETT: I'm sorry.	13:32:26
4	Objection to form.	13:32:28
5	A Depends how closely the comparison is.	13:32:29
6	For example, I would not compare to exendin. That	13:32:33
7	has a substantially different structure. It would	13:32:39
8	be very difficult to extrapolate doses.	13:32:42
9	I could compare to liraglutide, which	13:32:44
10	I've already indicated is so close in structure. So	13:32:46
11	its dosage range would inform the doses for the new	13:32:52
12	analog, in this case semaglutide.	13:32:55
13	Q At NIH, did you have any role in	13:33:04
14	approving clinical trials or designing clinical	13:33:08
15	trials?	13:33:09
16	A Yes, to both.	13:33:09
17	Q Including --	13:33:12
18	A First of all --	13:33:14
19	(Cross-talk.)	13:33:17
20	A Sorry, go ahead.	13:33:17
21	Q Including phase 2 trials?	13:33:18
22	A Yes, including phase 2 trials.	13:33:20

1 The trials that were done both -- when I 13:33:23
2 was scientific director, there were some so-called 13:33:29
3 intramural trials that were done, and I was involved 13:33:31
4 at several levels overseeing the intramural program 13:33:36
5 in such trials. 13:33:41

6 And not necessarily diabetes trials. One 13:33:43
7 that comes to mind was for hepatitis C, for example. 13:33:48
8 But -- an antiviral. 13:33:52

9 But as the institute director, 13:33:54
10 absolutely. And while the academic investigators 13:33:57
11 were -- the lead investigators at the various sites 13:34:01
12 are playing a combined role in designing the trial, 13:34:05
13 this is an iterative process in which the NIH 13:34:08
14 institute in question, in this case my institute, is 13:34:12
15 not merely an ATM machine, you know, doling out 13:34:14
16 money and here, go and do the trial. No. 13:34:18

17 I have -- my colleague Judy Fradkin, who 13:34:20
18 was the division director of the diabetes, 13:34:24
19 endocrinology, and metabolism, and she and I attend 13:34:27
20 all these trial meetings and were intimately 13:34:32
21 involved in the design of a variety of such trials, 13:34:36
22 yes. 13:34:38

1	Q	Have you ever had a phase 2 trial fail?	13:34:39
2		MR. ANSTAETT: Objection to form.	13:34:41
3	A	One of the trials that I just alluded to,	13:34:43
4		which is the hepatitis C trial, failed, yes,	13:34:46
5		absolutely, because of severe initially unrecognized	13:34:50
6		toxicity, yes.	13:34:56
7	Q	Have you ever had any phase 2 trials fail	13:34:58
8		in the diabetes space?	13:35:01
9		MR. ANSTAETT: Objection to form.	13:35:03
10	A	Not that I'm personally familiar with.	13:35:06
11		But the more generic question is, do	13:35:09
12		phase 2 trials ever fail. And I would have to	13:35:12
13		answer, yes. By definition, it's not yet a proven	13:35:15
14		therapy at that stage.	13:35:19
15	Q	Why do people run them if they know	13:35:22
16		they're going to fail?	13:35:25
17		MR. ANSTAETT: Objection to form.	13:35:26
18	A	Again, I come back to the reductio ad	13:35:27
19		absurdum.	13:35:36
20		You know why they run them? In hopes	13:35:36
21		that they'll develop a blockbuster drug that will be	13:35:38
22		successful and advance to phase 3 and then be	13:35:42

1 marketed and be extremely successful. 13:35:45

2 Recognizing that so many will fail 13:35:48

3 potentially, but what you have to understand is that 13:35:51

4 you can't get to the point of marketing without 13:35:55

5 going through these stages. That's at least the way 13:35:58

6 the drug approval process works. 13:36:01

7 So that's my understanding. 13:36:03

8 Q In your opinion, is liraglutide a 13:36:05

9 first-generation GLP-1 agonist? 13:36:07

10 A No. 13:36:10

11 Q What do you consider it? 13:36:11

12 A I consider the various exendin analogs as 13:36:15

13 first generation. And I'm not including here GLP-1 13:36:21

14 itself, which I alluded to earlier. The native 13:36:26

15 peptide was actually infused in individuals with 13:36:28

16 type 2 diabetes and had beneficial effects. But I 13:36:32

17 don't think anyone was serious about developing 13:36:35

18 that, so I wouldn't even call that first generation. 13:36:36

19 So I'd call the exendin analogs first 13:36:39

20 generation. 13:36:43

21 And then there was a recognition that 13:36:44

22 there are more efficacious analogs potentially 13:36:46

1 available closer in structure to authentic GLP-1 13:36:50
2 than exendin-4 is. It was quickly recognized, 13:36:54
3 though, that pharmacokinetics and half-life would be 13:36:58
4 an issue. 13:37:02

5 And so you saw parallel development of 13:37:04
6 liraglutide, albiglutide, dulaglutide, and others 13:37:06
7 all structured in a way to prolong their half-life 13:37:10
8 generally through binding. In the case of 13:37:17
9 albiglutide, overtly bound covalently to albumin. 13:37:19
10 In the case of dulaglutide, by covalently binding 13:37:26
11 GLP-1 itself to the FC fragment of IgG4 human. 13:37:30

12 And liraglutide is in that category. So 13:37:34
13 I would call it at least the second generation, 13:37:38
14 depending on how you want to define the generations. 13:37:44

15 Q Are you familiar with Bydureon? 13:37:47

16 A Somewhat. I'm aware that there are 13:37:52
17 exenatide extended release, and perhaps the trade 13:37:57
18 name is Bydureon. 13:38:01

19 Q And you understand that extended 13:38:04
20 release -- how is that achieved? How is it 13:38:07
21 different than Byetta? 13:38:09

22 A Frankly, I'm not sure. 13:38:13

1	Q	Are you aware that Bydureon is a	13:38:15
2		suspension?	13:38:19
3	MR. ANSTAETT:	Objection to form.	13:38:21
4		And Josh, I'm just going to put an	13:38:23
5		objection on the record that I think you're getting	13:38:27
6		pretty far afield from anything that's in the expert	13:38:29
7		report.	13:38:31
8	A	I'm aware that GLP-1 analogs may have	13:38:39
9		challenges as they're formulated with regard to	13:38:46
10		solubility.	13:38:48
11		And so in the case of semaglutide, for	13:38:50
12		example, we have the '833 patent which really	13:38:57
13		specifies a formulation in which it's suspended.	13:39:02
14		So I'm not positive about Bydureon, but I	13:39:06
15		would not be surprised if it is in a suspension	13:39:10
16		form.	13:39:13
17	Q	Would you consider liraglutide a	13:39:44
18		first-generation GLP-1 analog?	13:39:46
19	A	It's an arbitrary definition. I would	13:39:51
20		consider it a second-generation GLP-1 analog.	13:39:54
21	Q	Okay. But you're lumping together --	13:39:56
22		you're saying the first-generation GLP-1 analog was	13:39:59

1	exenatide.	13:40:02
2	Fair?	13:40:03
3	A For purposes of definition, as we're	13:40:04
4	discussing it, yes, fair.	13:40:06
5	Q Do you consider --	13:40:08
6	A And just to complete that thought, it's	13:40:09
7	also just historically in terms of time of	13:40:13
8	development. So exendin-4 was the first such GLP-1	13:40:17
9	receptor analog in development, circa 2004 or	13:40:25
10	thereabouts. And then you get a series, including	13:40:31
11	liraglutide, that are closer to the 2009 time range.	13:40:35
12	Q If you can turn to paragraph 296. Let me	13:40:42
13	know when you're there.	13:41:04
14	MR. ANSTAETT: And Josh, we've been going	13:41:09
15	an hour since we came back. And I don't want to cut	13:41:11
16	you off at all if we're close, but if we're not, I	13:41:13
17	might just need to take a short break.	13:41:17
18	MR. REICH: I think we're close, but if	13:41:19
19	you want to take a break.	13:41:21
20	MR. ANSTAETT: You don't have to do it	13:41:22
21	now. But if it's going to be, like, another half an	13:41:23
22	hour or another hour after this.	13:41:26

1	MR. REICH: No. I think we'll be on the	13:41:28
2	short.	13:41:32
3	MR. ANSTAETT: Okay.	13:41:33
4	A I do see 296, yes.	13:41:33
5	Q Okay. And you write here that, the	13:41:36
6	Goland declaration simply points generically to	13:41:40
7	journal reports of the SUSTAIN trials.	13:41:43
8	Do you see that?	13:41:46
9	A I do.	13:41:47
10	Q And you also write that these are just	13:41:48
11	straightforward presentations of favorable clinical	13:41:50
12	trial results, and that these are essentially Novo	13:41:54
13	Nordisk publications.	13:41:57
14	Do you see that?	13:41:59
15	A I do.	13:41:59
16	Q In your experience, aren't most clinical	13:42:03
17	trials funded by the brand?	13:42:07
18	MR. ANSTAETT: Objection to form.	13:42:11
19	A The answer is no. But again, depends on	13:42:14
20	the quantitation.	13:42:18
21	So most NIH-sponsored trials, of which	13:42:19
22	there are many, are not industry sponsored.	13:42:25

1 Industry may provide the drug gratis, but they are 13:42:29
2 most definitely not industry sponsored. 13:42:36

3 And what I am aware is an evolving 13:42:39
4 practice spearheaded by medical journals such as The 13:42:45
5 New England Journal and others, The Lancet, 13:42:50
6 insisting for much greater transparency and 13:42:52
7 disclosure because of the fear, justified or not, 13:42:56
8 that trials, as the SUSTAIN trials are, in which 13:43:01
9 there are co-authors from the same company that 13:43:05
10 makes the drug, in which there's a contract research 13:43:10
11 organization or writing organization which has 13:43:14
12 actually written the manuscript, may not in all 13:43:16
13 cases -- and I'm not implying here flagrant 13:43:20
14 violation of ethical scientific journalism -- but 13:43:25
15 may not -- may have biases and may not be fully 13:43:29
16 transparent. 13:43:33

17 So the concern is that -- this applies to 13:43:34
18 all SUSTAIN publications. It doesn't in any way 13:43:38
19 impugn, as in the give and take during Dr. Goland's 13:43:43
20 deposition, the veracity and honesty and high ethics 13:43:47
21 of academic investigators, nor even the company 13:43:51
22 employee investigators. 13:43:55

1 But it's very difficult to -- it's, you 13:43:57
 2 know, beating your own chest to say, gee, look, 13:44:02
 3 we're great. That is not a credible source of 13:44:05
 4 praise, in my opinion. 13:44:08

5 Q So you don't dispute the results of the 13:44:09
 6 SUSTAIN trials. 13:44:11

7 Fair? 13:44:13

8 A I think that is fair. To the extent that 13:44:15
 9 I've read through them, looked at the data, looked 13:44:18
 10 at the quality of the academic investigators and 13:44:21
 11 others involved, I don't dispute the results. 13:44:25

12 Q And you don't dispute that these are 13:44:28
 13 published in peer-reviewed journals? 13:44:30

14 A I certainly don't dispute that. 13:44:34

15 Q Some of them are fairly prestigious, 13:44:36
 16 correct, like The New England Journal of Medicine? 13:44:41

17 A That certainly is a prestigious journal, 13:44:46
 18 yes. 13:44:49

19 MR. REICH: I think we can go off the 13:44:56
 20 record, Dave, take five minutes to look through. 13:44:58

21 But I think we can wrap up -- 13:45:00

22 MR. ANSTAETT: Okay. 13:45:02

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1	MR. REICH: -- fairly shortly.	13:45:03
2	MR. ANSTAETT: Sounds good.	13:45:04
3	(Recess from 1:45 p.m. until 1:49 p.m.)	13:49:17
4	BY MR. REICH:	13:49:17
5	Q Dr. Spiegel, if you could turn to	13:49:25
6	paragraph 212 on page 73 of your declaration,	13:49:26
7	please. Let me know when you're there.	13:49:30
8	A I am.	13:49:34
9	Q So you write that Dr. Goland's recitation	13:49:37
10	of fact, you know, essentially is untestable.	13:49:42
11	Is that fair?	13:49:48
12	MR. ANSTAETT: Objection to form.	13:49:52
13	A The sentence does read that her bare	13:49:53
14	assertion that the fact is so, making the assertion	13:49:58
15	essentially untestable. And that is a fair	13:50:02
16	statement. And, just as an example, skepticism, she	13:50:04
17	doesn't really cite any testable evidence why one	13:50:09
18	would be skeptical, except for her own skepticism,	13:50:13
19	which lasted all of two months or thereabouts.	13:50:17
20	Q And you also point to her opinions on	13:50:20
21	long-felt need, correct?	13:50:24
22	MR. ANSTAETT: Objection to form.	13:50:25

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1	A	Yes, I do.	13:50:27
2	Q	Do you dispute any of the descriptions of	13:50:31
3		the prior art therapies Dr. Goland provided in her	13:50:36
4		declaration and the deficiencies related to each?	13:50:40
5		MR. ANSTAETT: Objection to form.	13:50:43
6	A	With regard to satisfying a long-felt	13:50:46
7		unmet need, I had several objections, some of which	13:50:52
8		have been stated before, but I'll restate them.	13:50:55
9		One was that I think that she effectively	13:50:59
10		ignored liraglutide, for example, with regard to	13:51:08
11		weight loss. She emphasized, as if this was	13:51:13
12		absolutely and totally unique to Ozempic, its	13:51:15
13		ability to cause weight loss.	13:51:21
14		And the other examples that she gave,	13:51:24
15		yes, there are definitely other anti -- or diabetes	13:51:27
16		therapeutics that cause weight gain, insulin being	13:51:33
17		very prominent. But she seemed reluctant to admit	13:51:36
18		that here was liraglutide, an example of an	13:51:41
19		effective treatment that also caused some degree of	13:51:44
20		weight loss. Certainly not weight gain.	13:51:47
21		The other objection to her arguments	13:51:50
22		about satisfying unfelt -- long unfelt [sic] need	13:51:55

1 was what I alluded to earlier, which is the blocking
2 patent issue. And it's my view that the '343 and
3 '122 patents effectively would have blocked other
4 entities from making semaglutide because it was
5 already disclosed in those patents.

6 Q Okay. I think I asked something slightly
7 different.

8 Dr. Goland provided descriptions of prior
9 art therapies and their effectiveness and side
10 effects.

11 Do you recall those opinions?

12 A I recall those opinions, and I think that
13 they were a very selective assortment tending to
14 emphasize ones with particularly negative
15 consequences, be it hypoglycemia, weight gain,
16 et cetera, and really taking it out of the context,
17 except in a very limited way, which she eventually
18 admitted to, that the semaglutide is within this
19 class of GLP-1 receptor agonists, arguably somewhat
20 more efficacious, but nonetheless, that would be the
21 appropriate framework for comparison in terms of
22 prior art.

1 Q Is it your understanding that 13:53:20
2 Dr. Goland's experience treating thousands of 13:53:22
3 patients over tens of years is not relevant evidence 13:53:24
4 to long-felt need? 13:53:27

5 MR. ANSTAETT: Objection to form. 13:53:30

6 A First of all, I certainly don't want to 13:53:34
7 in any way impugn Dr. Goland as an empathetic, 13:53:38
8 caring practicing physician. But for the purposes 13:53:45
9 of this legal engagement, I have to be candid. 13:53:50

10 And so while she undoubtedly has vast 13:53:56
11 experience in treating patients with diabetes, she 13:54:00
12 is one of many individuals. 13:54:05

13 I only need to come back to one of the 13:54:09
14 articles that she cited in terms of praise where a 13:54:11
15 Mass General female physician said, I don't consider 13:54:15
16 Ozempic a game changer. Dr. Goland said, I do 13:54:18
17 consider it a game changer. 13:54:22

18 So, you know, different people come at 13:54:24
19 this with different perspectives. 13:54:27

20 I don't think extraordinary weight should 13:54:31
21 be given to the fact that she undoubtedly has 13:54:34
22 experience as being the compelling test of whether 13:54:37

1 these really are deserving of praise, unexpected
2 results, satisfying long-felt unmet need.

3 Q I'm just trying to get at your opinion on
4 paragraph 212. So you had written that her
5 declaration is not supported by any evidence,
6 correct?

7 A Testable evidence, correct.

8 Q So just to be clear, do you not consider
9 her experience testable evidence because it's not
10 documented, or did you cast it aside because it was
11 just her experience? I'm trying to understand if
12 you disregarded her --

13 A I cast it aside because it constitutes
14 what we call an n-of-1. This is her experience as
15 an experienced clinician -- her opinion as an
16 experienced clinician, but comes back to what we
17 were saying earlier. Have we pulled many other
18 experience clinicians? And I just gave you, again,
19 an anecdotal example of a contrary opinion from -- I
20 don't know the experience of that Mass General
21 physician. Perhaps she's quite experienced.

22 (Reporter interruption.)

1 Q Little n, the letter, of 1. n-of-1 is a 13:56:22
2 term of art which means that, in this case, a single 13:56:29
3 individual is offering an opinion, maybe an 13:56:33
4 experienced individual, but in terms of the weight 13:56:35
5 of evidence that has to be taken in the larger 13:56:38
6 context. That's all I'm saying. 13:56:41

7 MR. REICH: I pass the witness. Dave? 13:56:47

8 MR. ANSTAETT: Okay. We'll just take a 13:56:49
9 short break. It won't be long at all. And five 13:56:51
10 minutes and we'll be back. 13:56:54

11 (Recess from 1:56 p.m. until 2:03 p.m.) 14:03:49

12 MR. ANSTAETT: We don't have any 14:03:49
13 questions for Dr. Spiegel. 14:03:51

14 MR. REICH: Thank you for your time, 14:03:53
15 Dr. Spiegel. Thank you, Lisa. Thank you, Kollin. 14:03:54

16 (Transcript orders discussed.) 14:03:58

17 COURT REPORTER: Thank you. That's all I 14:03:58
18 need.

19 (Off the record at 2:03 p.m.)
20
21
22

1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

2
3 I, Lisa V. Feissner, RDR, CRR and Notary
4 Public in and for the District of Columbia, do
5 hereby certify:
6

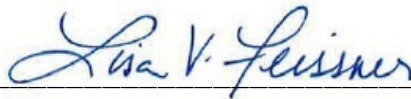
7 That ALLEN SPIEGEL, M.D., the witness
8 whose deposition is hereinbefore set forth, was duly
9 sworn by me before the commencement of such
10 deposition, and that such deposition was taken
11 before me and is a true record of the testimony
12 given by such witness.
13

14 I further certify that the adverse party,
15 MYLAN PHARMACEUTICALS INC., was represented by
16 counsel at the deposition.
17

18 I further certify that the deposition of
19 ALLEN SPIEGEL, M.D., occurred REMOTELY on FRIDAY,
20 JULY 26, 2024, commencing at 10:03 and concluding at
21 2:04.
22

1 I further certify that I am not related
2 to any of the parties to this action by blood or
3 marriage, I am not employed by or an attorney to any
4 of the parties to this action, and that I am in no
5 way interested, financially or otherwise, in the
6 outcome of this matter.

7
8 IN WITNESS WHEREOF, I have hereunto set
9 my hand this 30th day of JULY, 2024.

10
11
12 

13 NOTARY PUBLIC IN AND FOR
14 THE DISTRICT OF COLUMBIA
15 MY COMMISSION EXPIRES JUNE 15, 2028
16
17
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