

1 UNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD
3

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

7 vs

8 NOVO NORDISK A/S,
9 Patent Owner
10 -----

11 Case IPR2023-00724
12 U.S. Patent No. 10,335,462
13

14 Oral deposition of

15 MICHAEL J. BLAHA, M.D., M.P.H.
16

17 WASHINGTON, DC

18 WEDNESDAY, APRIL 10, 2024

19 9:07 a.m. EASTERN TIME
20

21 Job No.: 532166

22 Pages: 1 - 77

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

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2
3 Oral deposition of MICHAEL J. BLAHA, M.D.,
4 M.P.H., held at the offices of:

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C O N T E N T S

EXAMINATION OF MICHAEL J. BLAHA, M.D., M.P.H. PAGE

By Mr. White 5

By Mr. Reich 67

P R E V I O U S L Y

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

(Attached to transcript)

EXHIBITS PAGE

MPI Exhibit 1001 13

Novo Nordisk Exhibit 2055 7

Novo Nordisk Exhibit 2069 17

Novo Nordisk Exhibit 2086 43

Novo Nordisk Exhibit 2087 57

Novo Nordisk Exhibit 2090 45

Novo Nordisk Exhibit 2091 49

Novo Nordisk Exhibit 2092 49

Novo Nordisk Exhibit 2093 19

Novo Nordisk Exhibit 2101 33

Novo Nordisk Exhibit 2102 33

Novo Nordisk Exhibit 2109 30

Novo Nordisk Exhibit 2112 26

P R O C E E D I N G S

MICHAEL J. BLAHA, M.D., M.P.H.,

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

09:07:58

EXAMINATION

09:07:58

BY MR. WHITE:

09:07:58

Q Good morning, Dr. Blaha.

09:07:59

A Good morning.

09:08:00

Q Can you please state your name for the
record.

09:08:01

09:08:03

A Dr. Michael Joseph Blaha.

09:08:03

Q And who is your current employer?

09:08:05

A Johns Hopkins University.

09:08:07

Q Have you ever had your deposition taken
before?

09:08:10

09:08:11

A I have never had my deposition taken
before for -- I have for a medical case,
medical/legal case, but not for one of these
proceedings.

09:08:12

09:08:16

09:08:21

09:08:23

Q Okay. So I'll just go over a few of the
ground rules.

09:08:23

09:08:27

I'll try to ask clear questions, but if

09:08:28

1	there's something about my question you don't	09:08:30
2	understand, please let me know, and I'll try to	09:08:32
3	clarify or rephrase.	09:08:33
4	A Sounds good.	09:08:35
5	Q We should try to give verbal answers.	09:08:36
6	The court reporter will be taking everything down,	09:08:38
7	so if you just give a head nod or something, it will	09:08:40
8	be difficult for the court reporter.	09:08:43
9	I will try not to talk over you. If I	09:08:44
10	do, it's inadvertent. And I'd likewise ask that you	09:08:47
11	let me finish my question. That makes it easier for	09:08:50
12	the court reporter.	09:08:53
13	A Sure.	09:08:53
14	Q If I do cut you off, again, please let me	09:08:54
15	know, and I'll let you finish.	09:08:57
16	Your counsel may object from time to	09:08:58
17	time, but unless he instructs you not to answer, you	09:09:01
18	should try to answer the question.	09:09:03
19	Any time you need a break, just let me	09:09:08
20	know, I'm happy to take a break.	09:09:10
21	I understand you have a hard stop at 2:15	09:09:12
22	today. Is that right?	09:09:15

1	A	Yes.	09:09:17
2	Q	And you understand you're here today to	09:09:17
3		talk about the declaration you submitted in an IPR	09:09:20
4		related to the '462 patent?	09:09:24
5	A	Yes.	09:09:26
6		(Previously marked Exhibit 2055 attached	09:09:26
7		to the transcript.)	09:09:26
8		BY MR. WHITE:	09:09:26
9	Q	So I'm going to hand you what's already	09:09:32
10		been marked as Exhibit 2055.	09:09:34
11		So do you recognize 2055 as your	09:09:48
12		declaration?	09:09:50
13	A	I do.	09:09:50
14	Q	Do you have any corrections to your	09:09:51
15		declaration?	09:09:56
16	A	No corrections to this declaration.	09:09:57
17		There was one instance where, I guess, an exhibit	09:10:01
18		was an abbreviated version of an article rather than	09:10:05
19		the full PDF. I think that's already been	09:10:09
20		communicated. But other than that, this is correct.	09:10:11
21	Q	And so your declaration relates to the	09:10:14
22		'462 patent?	09:10:18

1	A	Correct.	09:10:19
2		MR. REICH: Object to the form.	09:10:20
3	Q	So that's U.S. Patent 10,335,462. If I	09:10:22
4		refer to that as the '462 patent, will you	09:10:27
5		understand what I'm referring to?	09:10:29
6	A	Yes.	09:10:30
7	Q	Your report addresses unexpected results	09:11:07
8		and industry praise.	09:11:10
9		Is that right?	09:11:11
10	A	Yes.	09:11:11
11	Q	And you're not offering opinions on the	09:11:12
12		ultimate obviousness or nonobviousness of the '462	09:11:16
13		patent, correct?	09:11:20
14		MR. REICH: I'm going to caution the	09:11:22
15		witness not to reveal the substance of any	09:11:23
16		communications with counsel.	09:11:25
17	A	I think everything that I've commented on	09:11:31
18		and what I opine on today is here in the report, so	09:11:34
19		we can refer back to the report.	09:11:39
20	Q	So if you turn to Exhibit B in your	09:11:40
21		declaration, that's your materials considered list.	09:11:43
22	A	E?	09:11:57

1	Q	B.	09:11:58
2	A	Oh, B.	09:12:00
3	Q	So Appendix B, does that include all the	09:12:01
4		materials you reviewed in preparing your	09:12:04
5		declaration?	09:12:06
6	A	Yes.	09:12:06
7	Q	You did not speak to any of Novo's other	09:12:07
8		witnesses.	09:12:12
9		Is that correct?	09:12:13
10	A	Correct.	09:12:13
11	Q	And you did not speak to any nonlawyer	09:12:13
12		Novo personnel.	09:12:18
13		Is that correct?	09:12:19
14	A	That's correct.	09:12:19
15	Q	And you did not review any of the Mylan	09:12:20
16		declarations that were submitted in this IPR.	09:12:24
17		Is that correct?	09:12:26
18	A	Correct.	09:12:26
19	Q	Is it correct that the only documents on	09:12:28
20		your materials considered list that are before July	09:12:37
21		of 2012 are Exhibits 2112, the Terry article, and	09:12:40
22		Exhibit 2113, the Victoza approval letter?	09:12:48

1 MR. REICH: Objection to form. 09:12:52

2 A I think we can just look through the 09:12:57

3 years to answer that question, which are all listed 09:13:00

4 here. And the years are all represented here, but I 09:13:04

5 see that Exhibit 2112 is 2012, and 2113 is 2010. 09:13:10

6 Q So on pages 6 to 8 of your declaration, 09:13:21

7 paragraphs 13 through 20, you have a Legal Standards 09:13:36

8 section. And that was provided to you by counsel, 09:13:41

9 correct? 09:13:44

10 A Yes. 09:13:45

11 Q And is this the -- paragraphs 13 through 09:13:46

12 20 set forth your complete understanding of the 09:13:54

13 legal standards? 09:13:58

14 A The legal standards -- I understand the 09:14:00

15 legal standards set out in 13 through 20. 09:14:05

16 Q And the legal standards in 13 through 20 09:14:07

17 are the -- are all of the legal standards you were 09:14:14

18 provided. 09:14:17

19 Is that correct? 09:14:18

20 A That's correct. 09:14:18

21 Q In forming the opinions that you offer in 09:14:19

22 your declaration, did you consider what was the 09:14:29

1	closest prior art to the '462 patent?	09:14:33
2	A When I reviewed -- when I opined upon	09:14:38
3	this case, I considered the state of the field	09:14:42
4	before 2012 for the patent, and I considered it	09:14:45
5	afterwards as well.	09:14:50
6	Q So my question was a little different.	09:14:52
7	Maybe it's a legal question, so we'll try and break	09:15:00
8	it down.	09:15:02
9	Do you understand that unexpected results	09:15:02
10	are evaluated in comparison to the closest prior	09:15:05
11	art?	09:15:09
12	MR. REICH: I'm going to object to form.	09:15:09
13	And I'm going to caution the witness to	09:15:10
14	not reveal the substance of any communication or	09:15:12
15	work -- communication with counsel or work product	09:15:15
16	in answering that question. But you can otherwise	09:15:17
17	answer.	09:15:19
18	A I feel like I generally understand the	09:15:20
19	meaning of "unexpected results."	09:15:22
20	Q And are unexpected results -- do you have	09:15:25
21	an understanding that they're based on comparison to	09:15:29
22	the closest prior art?	09:15:32

1	A	Yeah. I think I understand that	09:15:33
2		"unexpected" would mean that they wouldn't be	09:15:36
3		expected at the time that we're discussing and	09:15:38
4		afterwards. So they were unexpected.	09:15:43
5	Q	And as you prepared your declaration, did	09:15:46
6		you have an understanding of what the closest prior	09:15:50
7		art was to the invention claimed in the '462 patent?	09:15:52
8		MR. REICH: Object to form.	09:15:54
9	A	I read the patent as provided. We can	09:15:56
10		look at the patent. But that's what I understood.	09:15:59
11	Q	Did you consider liraglutide to be the	09:16:05
12		closest prior art to the '462 patent?	09:16:10
13		MR. REICH: Objection to form.	09:16:12
14	A	I didn't make any specific consideration.	09:16:12
15		I considered the field as a whole, which involves	09:16:14
16		diabetes and cardiovascular disease, and there's	09:16:17
17		lots of activity in that field.	09:16:20
18	Q	Earlier, you said when you opined in the	09:16:39
19		case, you considered the state of the field before	09:16:43
20		2012.	09:16:45
21		Did you review any articles before 2012	09:16:45
22		to evaluate the state of the field?	09:16:49

1	A	I -- I was a practicing physician at that	09:16:52
2		time, so I relied on my experience and my training,	09:16:56
3		my education about the state of the field before	09:17:01
4		that time, and my experience, training, clinical	09:17:03
5		practice for what came afterwards.	09:17:07
6	Q	So in forming your opinions in this case,	09:17:13
7		did you consider whether or not semaglutide was	09:17:57
8		already known in the prior art as of the priority	09:18:03
9		date?	09:18:06
10		MR. REICH: Objection to scope and form.	09:18:07
11	A	I read the patent, which was the basis of	09:18:08
12		my understanding of the discussion today.	09:18:11
13	Q	Did you have, in forming your opinions, a	09:18:15
14		view of whether or not semaglutide was already known	09:18:19
15		in the prior art as of the priority date?	09:18:21
16		MR. REICH: Objection to scope and form.	09:18:25
17	A	I believe I answered that in saying I	09:18:26
18		read the patent, and then my experience in the field	09:18:28
19		in treating diabetes and cardiovascular disease.	09:18:32
20		(Previously marked Exhibit 1001 attached	09:18:32
21		to the transcript.)	09:18:54
22	BY MR. WHITE:		09:18:54

1	Q	Just so you have it, I'm going to go	09:18:55
2		ahead and give you a copy of the Exhibit 1001, which	09:18:57
3		is the '462 patent.	09:19:03
4	A	Thank you.	09:19:04
5	Q	So other than -- you did review the '462	09:19:05
6		patent.	09:19:05
7		Did you review any other prior art to the	09:19:10
8		'462 patent?	09:19:12
9	MR. REICH:	Objection to form and scope.	09:19:14
10	A	I think the best way I can answer that	09:19:17
11		question is, I'm very familiar with this field.	09:19:19
12		I've been practicing in this field. I review	09:19:22
13		medical literature, use of medications, et cetera,	09:19:26
14		continuously throughout my practice and stay up to	09:19:30
15		date. And that would have been true before this	09:19:33
16		patent and afterwards as well.	09:19:36
17		And I also read this patent.	09:19:38
18	Q	As part of your normal practice, do you	09:19:40
19		review patent literature?	09:19:44
20	A	As part of my normal practice on a	09:19:45
21		day-to-day basis, I do not review patent literature,	09:19:47
22		no.	09:19:50

1	Q	In forming your opinions in this case,	09:19:50
2		did you have an understanding of whether or not	09:20:00
3		semaglutide was already described in the prior art	09:20:02
4		to be administered once weekly?	09:20:06
5		MR. REICH: Objection to form and scope.	09:20:09
6	A	May I ask for a rephrasing of that	09:20:13
7		question?	09:20:15
8	Q	Yeah. In forming your opinions in this	09:20:15
9		case, did you have an understanding of whether or	09:20:17
10		not once-weekly semaglutide was already disclosed in	09:20:19
11		the prior art?	09:20:21
12		MR. REICH: Same objections.	09:20:26
13	A	I think my best answer for this is, I've	09:20:27
14		read this patent, which my understanding is that	09:20:29
15		that's what we're discussing, and I understood this	09:20:31
16		patent and all the language -- and the key points	09:20:34
17		about this patent.	09:20:37
18	Q	I guess my question was a little bit	09:20:43
19		different.	09:20:46
20		I just want to understand what you	09:20:46
21		understood the state of the art was at the priority	09:20:48
22		date.	09:20:52

1 Did you have an understanding of whether 09:20:53
2 or not the state of the art as of the priority date 09:20:54
3 had already described semaglutide to be administered 09:20:57
4 once weekly? 09:21:01

5 A I guess -- I think, if I understand your 09:21:02
6 question, I can speak from my experience as an 09:21:04
7 expert in the field, as a clinician. 09:21:07

8 And I can say that at that time and the 09:21:10
9 way I was practicing, what I was aware of at the 09:21:14
10 time that -- roughly the year of this patent, I was 09:21:16
11 not aware of semaglutide. I'm not sure if that's 09:21:19
12 answering your question. 09:21:27

13 I'm very much aware of the state of the 09:21:28
14 art of treating cardiovascular disease and diabetes, 09:21:31
15 like I said, throughout the time period we're 09:21:34
16 talking about today. 09:21:36

17 Q So Ozempic is approved with a 09:21:49
18 0.5 milligram and a 1 milligram maintenance dose, 09:21:53
19 correct? 09:21:56

20 MR. REICH: Objection to form. 09:21:56

21 A Yeah, we can review the Ozempic label. 09:21:56
22 There is a 0.25 initial dose. There's a dose 09:22:00

1	escalation to the target dose of 1 milligram	09:22:05
2	subcutaneous weekly, which is the target dose that I	09:22:09
3	use in my practice. And I think the details are in	09:22:12
4	the label.	09:22:15
5	(Previously marked Exhibit 2069 attached	09:22:15
6	to the transcript.)	09:22:18
7	BY MR. WHITE:	09:22:18
8	Q And just so you have it, I'll give you a	09:22:18
9	copy of that label. This is what's been previously	09:22:20
10	marked as Novo's Exhibit 2069.	09:22:21
11	A Thank you.	09:22:21
12	Q You say the 1 milligram dose is the	09:22:44
13	target dose.	09:22:46
14	What do you mean by that?	09:22:48
15	MR. REICH: Objection to form.	09:22:49
16	A I can give some answers about the way	09:22:50
17	Ozempic is used in practice and the way it was used	09:22:52
18	in the pivotal trial that resulted in the approval	09:22:56
19	of this medication.	09:23:01
20	It's a subcutaneous weekly injection.	09:23:03
21	You usually start your patient at the lowest dose,	09:23:08
22	which is 0.25 milligrams, to ensure tolerability.	09:23:10

1 It's a dose titration. Usually, they stay at 0.25 09:23:14
 2 for at least a month. About four weeks is what I 09:23:18
 3 like to do to make sure that there's tolerance of 09:23:20
 4 the medication. 09:23:23

5 And then you titrate the dose towards a 09:23:23
 6 target dose of, in this case, 1 milligram, which is 09:23:27
 7 what was used in the clinical trials that resulted 09:23:30
 8 in cardiovascular benefit. 09:23:32

9 So you'd move to the 0.5 dose to ensure 09:23:34
 10 tolerance, and then you'd have a target of getting 09:23:38
 11 your patient on the 1 milligram dose where the 09:23:38
 12 cardiovascular benefit was observed. 09:23:40

13 Q Was there an observed cardiovascular 09:23:41
 14 benefit at 0.5 milligram dose? 09:23:43

15 A The preponderance of the cardiovascular 09:23:46
 16 benefit was observed at the 1 milligram dose. 09:23:50

17 Q Was there a cardiovascular benefit at the 09:23:52
 18 0.5 milligram dose? 09:23:54

19 A It was not statistically significant at 09:23:55
 20 the 0.5 milligram dose if you look at that 09:23:58
 21 individually. The 1 milligram dose showed greater 09:24:01
 22 cardiovascular benefit than the 0.5 dose. So I 09:24:04

1	shoot for the 1 milligram dose as a target.	09:24:07
2	Q And the 0.5 milligram dose is approved as	09:24:10
3	a maintenance dose for Ozempic, correct?	09:24:12
4	A Yes.	09:24:15
5	Q And it has been since Ozempic was first	09:24:16
6	approved.	09:24:19
7	Is that right?	09:24:19
8	A Yes. 0.25, 0.5, and 1 milligram doses	09:24:19
9	have all been approved, I believe, since the initial	09:24:24
10	approval date.	09:24:26
11	Q And a 2 milligram maintenance dose of	09:24:27
12	Ozempic, that was recently approved in March of	09:24:29
13	2022, I believe.	09:24:32
14	Is that right?	09:24:32
15	A That's correct. That came later, right.	09:24:33
16	(Previously marked Exhibit 2093 attached	09:24:33
17	to the transcript.)	09:25:19
18	BY MR. WHITE:	09:25:19
19	Q I'm going to hand you a copy of what's	09:25:28
20	been marked as Exhibit 2093.	09:25:30
21	So do you recognize Exhibit 2093 as the	09:25:36
22	Davies article that you discuss in your declaration?	09:25:38

1 A As of the early 2010s, using
2 glucose-lowering drugs as a category was the
3 standard of care for type 2 diabetes, but there were
4 serious concerns with the cardiovascular safety of
5 these drugs, as in glucose-lowering drugs.

6 So that theme is present in the review
7 article, that there's concern about diabetes drugs
8 at the time, which we referred to as
9 glucose-lowering drugs, and their cardiovascular
10 safety.

11 Q Is there anything in Davies that
12 specifically references a concern about GLP-1
13 receptor agonists?

14 A I'd have to read the words carefully to
15 recall that. But I think that's not the point I'm
16 making here.

17 The point I'm making here is that there
18 was a concern in general in the field, which was
19 very pervasive at the time, because there was -- it
20 was unknown if you could treat diabetes, per se,
21 type 2 diabetes and lower glucose and lower
22 cardiovascular events, or do you actually cause

1	cardiovascular events. So this was a debate in the	09:27:59
2	field. It was very much a real thing at the time.	09:28:01
3	So that's what I'm referring to here.	09:28:05
4	Q I understand that. I guess what -- I	09:28:07
5	just wanted to see if there was anything in	09:28:09
6	Exhibit 2093 that you're aware of that specifically	09:28:12
7	references a concern about GLP-1 receptor agonists.	09:28:15
8	MR. REICH: Objection to form.	09:28:20
9	A I guess what I would say is that since	09:28:21
10	GLP-1 receptor agonists are glucose-lowering drugs,	09:28:24
11	and this refers to the general concept of glucose	09:28:28
12	lowering and concern about cardiovascular safety,	09:28:31
13	that I would take the article to include concerns	09:28:33
14	about any strategy for glucose-lowering drugs at	09:28:37
15	this time and cardiovascular risk.	09:28:43
16	Q So if you could look at the second page	09:28:58
17	of Davies.	09:29:00
18	A Sure.	09:29:01
19	Q When I refer to page numbers, I'm going	09:29:03
20	to refer to how it's been marked on the bottom.	09:29:06
21	All right?	09:29:08
22	A Okay. Page 2. Got it.	09:29:08

1	Q	So if you look at the left-hand column of	09:29:10
2		the first full paragraph that begins with, Until	09:29:15
3		around a decade ago. It says, Until around a decade	09:29:17
4		ago, the standard of care for type 2 diabetes	09:29:22
5		involved use of glucose-lowering drugs such as	09:29:24
6		metformin, sulfonylureas, thiazolidinediones,	09:29:24
7		meglitinides and alpha-glucosidase inhibitors.	09:29:47
8	A	Mm-hmm.	09:29:47
9	Q	I probably mispronounced a few of those.	09:29:47
10	A	That's okay.	09:29:50
11	Q	So were those the categories of drugs	09:29:51
12		that were the standard of care in the 2010s for	09:29:53
13		lowering glucose?	09:29:57
14	MR. REICH:	Objection to form and scope.	09:29:58
15	A	I would say that around, you know -- this	09:29:59
16		makes a very general statement in this article,	09:30:03
17		around a decade ago. But I would say around 2010 or	09:30:05
18		before -- maybe up until 2010, yeah, the standard of	09:30:11
19		care for treating type 2 diabetes would be	09:30:15
20		metformin, sulfonylureas, as you mentioned,	09:30:19
21		thiazolidinediones or TZDs, meglitinides,	09:30:24
22		alpha-glucosidase inhibitors.	09:30:26

1 All of these were in the armamentarium 09:30:31
2 for trying to lower glucose in type 2 diabetes, and 09:30:33
3 at the time, there was not a lot of way to 09:30:37
4 prioritize these. We just had a lot of options for 09:30:39
5 lowering glucose. 09:30:42

6 And none of these were -- lowered 09:30:43
7 cardiovascular events. In fact, there was concern 09:30:50
8 about their cardiovascular safety. So this was kind 09:30:52
9 of the array of drugs that were available at that 09:30:54
10 time that were used most often. 09:30:56

11 Q So in paragraph 25, you also reference a 09:31:24
12 2008 FDA mandate. 09:31:28

13 A Right. 09:31:30

14 Q Did you review the 2008 FDA guidance 09:31:30
15 prior to your report? 09:31:35

16 A For preparing this report, I didn't 09:31:35
17 review that. I'm very familiar with that. I'm very 09:31:38
18 familiar with that guidance because of my experience 09:31:43
19 with FDA, experience with reviewing the literature 09:31:47
20 throughout my time in this field. 09:31:50

21 So I didn't re-review that. But I'm very 09:31:53
22 familiar with the idea that's commonly known in my 09:31:55

1 field that the 2008 guidance led to these 09:31:58

2 cardiovascular outcome trials, which we'll probably 09:32:00

3 talk about today, to assess cardiovascular safety 09:32:03

4 for diabetes drugs. 09:32:05

5 Q Do the 2008 FDA guidance reference a 09:32:06

6 specific concern about GLP-1 receptor agonists? 09:32:10

7 MR. REICH: Objection to form. 09:32:13

8 A The 2008 guidance was very important. I 09:32:13

9 think what it does is it reflects the concern at the 09:32:18

10 time that glucose lowering in type 2 diabetes could 09:32:21

11 cause cardiovascular harm, including some concern 09:32:25

12 for major adverse cardiovascular events or heart 09:32:28

13 failure. 09:32:32

14 So the guidance tried to make statements 09:32:33

15 that glucose-lowering drugs should be tested for 09:32:36

16 their cardiovascular safety in general. 09:32:40

17 Q I think my question was a little bit 09:32:43

18 different. 09:32:46

19 Did you recall whether the 2008 FDA 09:32:46

20 guidance reflected a specific concern about GLP-1 09:32:50

21 receptor agonists? 09:32:54

22 MR. REICH: Objection to form. 09:32:55

1 A I don't believe that the purpose of that
2 document was to call out any particular class of
3 drugs in any particular way, but to say in general,
4 type 2 diabetes drugs, since there have been signals
5 of concern for cardiovascular harm, need to be
6 tested to ensure their safety to stay in the
7 marketplace.

8 (Previously marked Exhibit 2112 attached
9 to the transcript.)

10 BY MR. WHITE:

11 Q So I've handed you what's been previously
12 marked as Exhibit 2112.

13 Do you recognize this as the Terry
14 article that you discuss in paragraph 26?

15 A Yes.

16 Q And you cite this article for the
17 proposition that there were significant pessimism
18 about the possibility of observing significant
19 reductions in MACE simply by improving HbA1c and
20 especially with GLP-1 receptor agonists.

21 Is that right?

22 A Yes.

1 Q Does the Terry article, Exhibit 2112, 09:34:59
2 specifically address GLP-1 receptor agonists? 09:35:02

3 A So the title of the article is 09:35:07
4 interesting. It talks about, does aggressive 09:35:08
5 glucose control benefit macrovascular and 09:35:11
6 microvascular disease in type 2 diabetes, speaking 09:35:16
7 to the concern at the time that, you know, there 09:35:16
8 might be cardiovascular risk by trying to lower 09:35:21
9 someone's blood glucose too much. 09:35:23

10 So the idea was, you know, we need to 09:35:26
11 treat diabetes and lower cardiovascular disease, but 09:35:28
12 does aggressive lowering of glucose actually prevent 09:35:31
13 cardiovascular outcomes. 09:35:35

14 So I think the main purpose of this 09:35:36
15 article was to talk about that general concept of, 09:35:38
16 you know, lowering glucose, treating diabetes, is 09:35:43
17 there any cardiovascular benefit. 09:35:45

18 Now, as far as trying to call out 09:35:47
19 specific drug classes, I don't think that was the 09:35:52
20 main purpose of this article is to say that any 09:35:55
21 particular drug class has more risk than another, 09:35:57
22 rather than speaking to aggressive glucose lowering 09:36:02

1 in general. 09:36:04

2 And since GLP-1s are strong reducers of 09:36:05
3 glucose in A1C, I think that would be part of the 09:36:11
4 consideration of aggressive glucose lowering. 09:36:14

5 But as far as direct reference to GLP-1s, 09:36:16
6 I would have to take some time to re-review the 09:36:23
7 article to see if there's a specific reference to 09:36:26
8 GLP-1s or just the concept of what GLP-1s do, 09:36:28
9 aggressive glucose lowering. 09:36:32

10 Q The first sentence of paragraph 26 ends 09:36:34
11 with -- after expressing that pessimism, there's, 09:36:37
12 especially with using GLP-1 receptor agonists. 09:36:41

13 So what I was trying to understand is, 09:36:46
14 what in Terry especially calls out GLP-1 receptor 09:36:48
15 agonists? 09:36:52

16 A I think I understand your question. 09:36:52

17 I take to this mean, is there a concern 09:36:54
18 with aggressive glucose lowering and strategies to 09:36:59
19 aggressively lower glucose. 09:37:03

20 And one of the strategies that we know 09:37:05
21 about to aggressively lower glucose, you know, at 09:37:07
22 the present time, we understand that to be, for 09:37:12

1 example, like a GLP-1 which aggressively lowers
2 glucose.

3 So it's more of the strategy about
4 aggressively lowering glucose through a variety of
5 tactics, does that lower -- and it's posed as a
6 question, does aggressive glucose lowering lower
7 macrovascular and microvascular events,
8 cardiovascular events in the case of macrovascular
9 disease, in general.

10 I think that was a lot of the question
11 that was being asked at the time.

12 So I take that -- what I take my sentence
13 here to mean is that aggressive strategies for
14 lowering glucose, there was significant concern for
15 really all of them, including, of course, GLP-1
16 receptor agonists, which are aggressive
17 glucose-lowering drugs, and their risk for major
18 adverse cardiovascular events, which is the
19 macrovascular events.

20 Q So there's nothing you can point me to in
21 Terry that specifically calls out GLP-1 receptor
22 agonists?

1 MR. REICH: Objection to form. 09:38:20

2 Q Is that fair? 09:38:21

3 A I think what I was saying sort of 09:38:24

4 encapsulates the thought here about aggressive 09:38:28

5 glucose lowering and the idea of aggressive glucose 09:38:30

6 lowering, is that good for microvascular events and 09:38:34

7 macrovascular events. Really, any strategy for 09:38:36

8 aggressive glucose lowering, which can include 09:38:40

9 insulin, other things, and as we know, GLP-1s are 09:38:42

10 aggressive glucose-lowering drugs. 09:38:47

11 So I think it's a -- the concept that's 09:38:49

12 in this paper informed my -- informed the sentence 09:38:53

13 there. 09:38:58

14 (Previously marked Exhibit 2109 attached 09:38:58

15 to the transcript.) 09:39:18

16 BY MR. WHITE: 09:39:18

17 Q So I've handed you what's been previously 09:39:30

18 marked as Exhibit 2109. 09:39:32

19 Do you recognize this as the Sattar 09:39:35

20 article that you reference in paragraph 26? 09:39:38

21 A Yes. Naveed Sattar, yeah. 09:39:42

22 Q Does this Sattar article specifically 09:39:56

1 describe any concern with respect to GLP-1 receptor 09:39:58
2 agonists specifically? 09:40:03

3 MR. REICH: Objection to form. 09:40:04

4 A Yeah, so the reference here to the Sattar 09:40:04
5 article that I have in my report refers to -- and 09:40:07
6 there's a quotation here. It says, As late as 2017, 09:40:13
7 cardiologists paid little attention to type 2 09:40:17
8 diabetes therapies, likely because until shortly 09:40:21
9 before type 2 diabetes therapies other than 09:40:23
10 metformin had little obvious favorable effect on 09:40:26
11 cardiovascular outcomes, which is the principal 09:40:27
12 cause of morbidity and mortality in type 2 diabetes. 09:40:29

13 So the reference here refers to this idea 09:40:33
14 that cardiologists paid little attention to diabetes 09:40:37
15 therapies because there was no cardiovascular 09:40:41
16 benefit. 09:40:43

17 Q Is there anything in Sattar that you can 09:40:43
18 point me to that specifically calls out a concern 09:40:45
19 about GLP-1 receptor agonists? 09:40:48

20 MR. REICH: Objection to form. 09:40:51

21 A Can you maybe expand upon your question? 09:40:56
22 What do you mean by "concern"? I think it 09:40:59

1	summarizes the field.	09:41:02
2	Q Is there anything in Sattar that	09:41:03
3	specifically points to a concern about GLP-1	09:41:05
4	receptor agonists causing cardiovascular injury?	09:41:09
5	A Cardiovascular injury. I think -- I	09:41:15
6	mean, I'm looking at Table 1 here. It summarizes	09:41:17
7	the data, for example, on two GLP-1 trials. So it	09:41:20
8	summarizes the data in the field.	09:41:25
9	Q And does anything in that table show a	09:41:31
10	concern in the field with respect to using GLP-1	09:41:37
11	receptor agonists with respect to cardiovascular	09:41:42
12	injury or increasing cardiovascular risk?	09:41:44
13	MR. REICH: Objection to form.	09:41:47
14	A You know, looking at the, you know,	09:41:47
15	cardiovascular end points, which I'm sure we'll	09:41:49
16	probably talk more about later, in SUSTAIN-6, there	09:41:51
17	was -- for example, you know, there's a large	09:41:54
18	reduction in MACE events in SUSTAIN-6, 26 percent.	09:41:56
19	Smaller, about half as much, in LEADER, 13 percent.	09:42:00
20	So there was a reduction in major	09:42:04
21	adverse -- I'm sure we'll talk about that --	09:42:07
22	cardiovascular events. So it summarized the data.	09:42:09

1	As far as MACE events, there was a reduction in MACE	09:42:11
2	events in those trials.	09:42:14
3	(Previously marked Exhibits 2101 and 2102	09:42:14
4	attached to the transcript.)	09:43:15
5	BY MR. WHITE:	09:43:15
6	Q So I'm going to give you Exhibit 2101.	09:43:24
7	And at the same time, I'll give you a copy of 2102.	09:43:30
8	A Okay.	09:43:36
9	Q So do you recognize Exhibit 2101 as the	09:43:47
10	publication of the SUSTAIN-6 trial?	09:43:52
11	A Yes. Anyone in my field would recognize	09:43:55
12	this one.	09:43:57
13	Q And 2102 is the supplementary appendix to	09:43:58
14	the SUSTAIN-6 publication?	09:44:04
15	A Yeah, to the original New England Journal	09:44:04
16	publication, yeah.	09:44:08
17	Q So SUSTAIN-6 was funded by Novo Nordisk.	09:44:09
18	Is that right?	09:44:13
19	A Yeah. It was the mandated cardiovascular	09:44:14
20	safety trial that they had to do for the study to	09:44:16
21	show cardiovascular safety.	09:44:20
22	Q And the purpose of SUSTAIN-6 was to	09:44:22

1 demonstrate safety, correct? 09:44:24

2 A You know, the reason why the FDA mandated 09:44:27
3 studies like this was to demonstrate cardiovascular 09:44:31
4 safety, yeah. 09:44:33

5 Q SUSTAIN-6 compared semaglutide at 09:44:34
6 0.5 milligrams and 1 milligram to placebo. 09:44:39

7 Is that right? 09:44:43

8 MR. REICH: Objection to form. 09:44:43

9 A Yeah, so this study looked on top of 09:44:44
10 standard of care for type 2 diabetes and randomized 09:44:46
11 patients to a placebo injection or dose escalation 09:44:50
12 of semaglutide subcutaneous dose weekly starting at 09:44:53
13 the 0.25 that we talked about, the starting dose, 09:44:57
14 and then dose escalating to 0.5 or 1 milligram 09:44:59
15 target dose, and then evaluated cardiovascular 09:45:06
16 outcomes. 09:45:09

17 Q So SUSTAIN-6 did not compare semaglutide 09:45:21
18 to liraglutide. 09:45:23

19 Is that right? 09:45:26

20 A That's correct. It was compared to 09:45:27
21 placebo. 09:45:29

22 Q And so the cardiovascular outcome trial 09:45:32

1	for liraglutide, that's LEADER, correct?	09:45:36
2	A Correct.	09:45:40
3	MR. REICH: Objection to form.	09:45:39
4	Give me a second to --	09:45:39
5	THE WITNESS: Sorry.	09:45:43
6	Q You didn't review the LEADER publication	09:45:43
7	in preparing your declaration, did you?	09:45:48
8	A I just reviewed the stuff that's listed	09:45:51
9	here. I will say that the LEADER trial is	09:45:54
10	well-known in my field of cardiovascular disease and	09:45:57
11	diabetes.	09:46:00
12	Q So the SUSTAIN-6 and LEADER trials	09:46:02
13	involved different patient populations.	09:46:04
14	Is that right?	09:46:07
15	MR. REICH: Objection to form.	09:46:08
16	A Yeah. And they're well-detailed in the	09:46:09
17	reports that they're separate trials.	09:46:11
18	Q And the LEADER trial was a much longer	09:46:13
19	trial than SUSTAIN-6.	09:46:16
20	Is that right?	09:46:17
21	MR. REICH: Objection to form.	09:46:18
22	A I mean, we could review the length of	09:46:19

1 time of follow-up of these trials, which is listed 09:46:21
 2 here. There's different -- trials are different in 09:46:24
 3 many regards. There was not exactly the same 09:46:29
 4 follow-up, no. 09:46:31

5 Q SUSTAIN-6 does not report that 09:46:58
 6 semaglutide is superior to liraglutide. 09:47:00

7 Is that fair? 09:47:05

8 A I guess I'll just summarize again kind of 09:47:06
 9 the main purpose of this trial. Once again, it was 09:47:09
 10 to try to demonstrate the cardiovascular safety, you 09:47:12
 11 know, or superiority, as it turns out, of 09:47:16
 12 semaglutide in this case versus placebo on top of 09:47:20
 13 standard of care for type 2 diabetes. So that was 09:47:23
 14 the purpose of this trial. 09:47:24

15 And the comparator, ultimately, like many 09:47:27
 16 randomized controlled clinical trials, was placebo 09:47:31
 17 versus semaglutide for cardiovascular outcomes over 09:47:34
 18 the course of the trial. 09:47:35

19 Did I answer your question? 09:47:37

20 Q So both LEADER and SUSTAIN-6 showed a 09:48:44
 21 decrease in three-point MACE. 09:48:48

22 Is that right? 09:48:52

1	MR. REICH: Objection, form.	09:48:52
2	A Yeah, I guess it's best just to review	09:48:53
3	each trial independently because they're independent	09:48:57
4	trials.	09:48:58
5	In front of me right now, I have	09:49:00
6	SUSTAIN-6. SUSTAIN-6 showed a 26 -- the primary	09:49:02
7	outcome was MACE, major adverse cardiovascular	09:49:06
8	events, which is a combination of myocardial	09:49:09
9	infarction or heart attack, stroke, or	09:49:18
10	cardiovascular death. That's what we call	09:49:23
11	three-point MACE.	09:49:25
12	And SUSTAIN-6, that was the study of	09:49:28
13	semaglutide subcutaneous, you know, target dose of	09:49:31
14	1 milligram showed a 26 percent reduction in	09:49:36
15	three-point MACE. So there was a reduction in	09:49:42
16	cardiovascular events, which I think was part of	09:49:44
17	your question.	09:49:46
18	The LEADER study was a separate trial,	09:49:47
19	which, you know, I did not refer to here, but is	09:49:50
20	well-known in the field that that trial, which was	09:49:54
21	also a study of three-point MACE, and we saw it a	09:49:57
22	second ago in that table, showed a reduction in	09:50:02

1 cardiovascular events of smaller magnitude, 09:50:04

2 13 percent on three-point MACE. 09:50:07

3 Does that answer your question? 09:50:09

4 Q Yeah, I think so. 09:50:10

5 So both of the trials had the same type 09:50:12

6 of effect in terms of reduction of three-point MACE? 09:50:15

7 MR. REICH: Objection to form. 09:50:20

8 A Yeah, I can't -- I don't think it's 09:50:21

9 accurate to say "the same type of effect." We 09:50:22

10 wouldn't use that language. We would just compare 09:50:25

11 the numbers and compare the results rather than just 09:50:26

12 generalize and say "type" or whatever. 09:50:29

13 And I would just summarize by saying 09:50:31

14 there was a 26 percent reduction in three-point MACE 09:50:33

15 in the SUSTAIN-6 trial, and there was a 13 percent 09:50:38

16 reduction in the LEADER trial, you know, and we 09:50:40

17 would compare those trials and say which one -- or 09:50:44

18 if we chose to compare them, we'd look at those 09:50:47

19 numbers and make a comparison. 09:50:50

20 So they both were similar trials, and 09:50:52

21 they were cardiovascular outcome trials, CVOTs, 09:50:56

22 which sometimes I'll refer to, cardiovascular 09:50:58

1 outcome trials.

09:50:56

2 They were separate trials that showed,
3 you know, the results that they showed, and I
4 summarize them. 26 percent reduction here,
5 SUSTAIN-6, and 13 percent reduction in the LEADER
6 study.

09:51:01

09:51:04

09:51:08

09:51:11

09:51:13

7 So they both were similar trials but, you
8 know, they're different trials. And if we were to
9 look at the different results, we would look at
10 those results that I just summarized there, which
11 are summarized in this paper for semaglutide.

09:51:13

09:51:16

09:51:19

09:51:21

09:51:24

12 Q So there was a different degree of
13 three-point MACE reduction in SUSTAIN-6 versus
14 LEADER?

09:51:27

09:51:33

09:51:37

15 MR. REICH: Objection to form.

09:51:37

16 A Again -- I mean, once again, when a
17 physician looks at these data, we don't use terms
18 like "degree" or something like that. We would look
19 at the data and really examine the data, because
20 that's really what should drive decision-making.

09:51:38

09:51:43

09:51:46

09:51:48

09:51:50

21 And we would look to summarize these
22 trials very simply, although they're complicated.

09:51:53

09:51:55

1	One had a 26 percent reduction; one had a 13 percent	09:51:57
2	reduction and a similar three-point MACE outcome.	09:52:01
3	Q Is it fair to say that you can't directly	09:52:04
4	compare the 26 percent reduction and the 13 percent	09:52:06
5	reduction in SUSTAIN-6 and LEADER?	09:52:09
6	A That's an interesting question.	09:52:12
7	So, of course, any physician has to	09:52:14
8	ultimately make medical decisions and, you know, at	09:52:17
9	least qualitatively or semi-qualitatively compare	09:52:23
10	trial results.	09:52:27
11	Like I said, there was a 26 percent	09:52:28
12	reduction in one and a 13 percent reduction in the	09:52:31
13	other.	09:52:34
14	But from a statistical point of view,	09:52:34
15	since they're separate trials, as is well known, you	09:52:36
16	can't make a direct comparison between two drugs	09:52:39
17	across two different trials. That would be	09:52:41
18	something inappropriate to do in a statistical point	09:52:42
19	of view.	09:52:45
20	But from a medical decision point of	09:52:46
21	view, we're always looking at different trials and	09:52:48
22	looking at our options.	09:52:50

1 When I take the bottom line for these 09:52:52
2 trials, I see a 26 percent reduction in SUSTAIN-6 09:52:54
3 and a 13 percent reduction in the other one, the 09:52:57
4 LEADER trial. 09:53:01

5 Q So in paragraph 43, you reference DPP-4 09:53:05
6 inhibitors. 09:53:21

7 Do you see that paragraph? 09:53:22

8 A Got it, okay. 09:53:22

9 Q And so DPP-4 inhibitors are an entirely 09:53:24
10 different class than GLP-1 receptor agonists. 09:53:28

11 Is that fair? 09:53:31

12 MR. REICH: Objection to form. 09:53:32

13 A I would say, yeah, we could list the 09:53:33
14 different classes of drugs. DPP-4 inhibitors, if 09:53:35
15 you were to group them together, it would be 09:53:38
16 distinct in their mechanism compared to GLP-1 09:53:38
17 receptor agonists. I consider them different drugs, 09:53:42
18 yeah. 09:53:44

19 Q And was it known that GLP-1 receptor 09:53:59
20 agonists would result in greater concentrations of 09:54:06
21 GLP-1 than DPP-4 agonists? 09:54:11

22 MR. REICH: Objection to form. 09:54:15

1	Q	Sorry, DPP-4 inhibitors?	09:54:16
2		MR. REICH: Objection to form and scope.	09:54:19
3	A	I didn't comment on, you know, the	09:54:20
4		details of the mechanisms and the finer points on	09:54:21
5		the mechanisms of these drugs other than the name of	09:54:24
6		the drugs specifies they have different mechanisms	09:54:27
7		of action. The name of the drug classes are the	09:54:29
8		mechanism.	09:54:32
9		But I didn't opine upon details about,	09:54:33
10		you know, incretin hormones going up or down and	09:54:38
11		things like that, just a general class of drugs.	09:54:41
12	Q	Were GLP-1 receptor agonists known to	09:54:43
13		have a greater effect on losing body weight than	09:54:45
14		DPP-4 inhibitors?	09:54:49
15		MR. REICH: Objection to form and scope.	09:54:50
16	A	You know, maybe you can rephrase your	09:54:52
17		question about -- I don't even know when you're	09:54:56
18		talking about, I guess. Rephrase that question.	09:54:59
19	Q	Was it known that GLP-1 receptor agonists	09:55:02
20		had a -- caused a greater reduction of body weight	09:55:04
21		than DPP-4 inhibitors?	09:55:09
22		MR. REICH: Same objections.	09:55:10

1	A	I'm similarly confused about the time	09:55:11
2		frame, I guess, or what we're talking about.	09:55:14
3		But I guess I'll just stick with what I	09:55:16
4		wrote here, which refers to cardiovascular safety or	09:55:18
5		cardiovascular benefit of these drugs.	09:55:22
6		(Previously marked Exhibit 2086 attached	09:55:22
7		to the transcript.)	09:56:04
8	BY MR. WHITE:		09:56:04
9	Q	I've handed you what's been marked as	09:56:15
10		Exhibit 2086.	09:56:17
11		Do you recognize this as the Abdul-Ghani	09:56:20
12		article that you cite in paragraph 46?	09:56:25
13	A	Yes. This looks like it, yeah.	09:56:27
14	Q	So in paragraph 46, you cite this article	09:56:34
15		for the proposition that we are entering into a new	09:56:37
16		era of type 2 diabetes management, right?	09:56:40
17	A	That's correct.	09:56:42
18	Q	And that new era wasn't ushered in	09:56:44
19		specifically by semaglutide, right?	09:56:49
20	MR. REICH:	Objection to form.	09:56:51
21	A	Yeah, I disagree. So my understanding of	09:56:52
22		kind of the wave, the new wave, let's call it a	09:56:57

1 paradigm shift, particularly in cardiologists in 09:57:02
2 thinking about treating diabetes to reduce 09:57:05
3 cardiovascular events really followed SUSTAIN-6 and 09:57:07
4 the clinically meaningful reduction MACE end points 09:57:14
5 that occurred in this SUSTAIN-6 trial that we talked 09:57:19
6 about. 09:57:21

7 So I don't agree that it has nothing to 09:57:22
8 do with semaglutide. 09:57:28

9 Q So on page 1, at the bottom of the 09:57:34
10 left-hand -- I guess the left-hand column, second to 09:57:38
11 last line starts, These studies make it clear that 09:57:44
12 we are entering into a new era in type 2 diabetes 09:57:47
13 management. 09:57:51

14 Do you see that? 09:57:52

15 A Yes, I do see that. 09:57:53

16 Q So the studies it refers to are both for 09:57:55
17 SGLT-2 inhibitors and GLP-1 receptor agonists, 09:58:00
18 right? 09:58:06

19 MR. REICH: Objection to form. 09:58:06

20 A It's a complicated question. 09:58:08

21 You know, you could see earlier in the 09:58:09
22 paragraph, you know, they talk about GLP-1 09:58:11

1	specifically. You can see the SUSTAIN-6 there	09:58:13
2	referenced. And they sort of talk about the field	09:58:15
3	in general.	09:58:18
4	They say, Together with EMPA-REG, that	09:58:19
5	was with the SGLT-2 inhibitor, IRIS, which is	09:58:24
6	actually with the thiazolidinedione. I think	09:58:26
7	they're taking about the general state of the field	09:58:29
8	at the time, including all of these trials that were	09:58:31
9	listed. If that answers your question.	09:58:34
10	Q Sure.	09:58:36
11	A It lists all of them there, many of them.	09:58:36
12	(Previously marked Exhibit 2090 attached	09:58:36
13	to the transcript.)	09:59:14
14	BY MR. WHITE:	09:59:14
15	Q So I've handed you what's been marked as	09:59:44
16	Exhibit 2090.	09:59:46
17	Do you recognize this as the 2019	09:59:49
18	European Society of Cardiology guidelines?	09:59:52
19	A Yes.	09:59:55
20	Q So if we refer to that as the ESC	09:59:58
21	guidelines, will you understand what I'm referring	10:00:02
22	to?	10:00:04

1	A	Yes.	10:00:04
2	Q	So the ESC guidelines recommend three	10:00:05
3		different GLP-1 receptor agonists in patients with	10:00:11
4		type 2 diabetes and cardiovascular disease or at	10:00:14
5		risk for cardiovascular disease, right?	10:00:19
6	A	Can you point me to where you're looking?	10:00:20
7	Q	Sure. So you cite pages 10 and 26.	10:00:22
8	A	Obviously, these guideline documents are	10:00:39
9		very large.	10:00:41
10		10, I guess, here in the lower right	10:00:43
11		corner. Okay. So this is a set of -- in a clinical	10:00:45
12		guideline, these color-coded things are a set of	10:00:52
13		recommendations.	10:00:54
14		I'm sorry. And your question?	10:00:56
15	Q	So these guidelines recommend	10:00:58
16		liraglutide, dulaglutide, and semaglutide in	10:01:03
17		patients with type 2 diabetes and cardiovascular	10:01:08
18		disease or are at risk for cardiovascular disease,	10:01:10
19		right?	10:01:12
20	A	Yeah, so this guideline is important	10:01:13
21		because it's one of the first that really started	10:01:15
22		to -- reflected the paradigm shift of treating	10:01:17

1 diabetes with an eye to avoiding cardiovascular 10:01:22
2 risk. 10:01:24

3 Like many guidelines, it doesn't try to 10:01:25
4 make specific recommendations, you have to use this 10:01:28
5 particular therapy. It says you should use a 10:01:30
6 therapy with proven cardiovascular benefits. 10:01:33

7 So yeah, it lists the therapies that 10:01:35
8 have, at the time of this document, proven 10:01:38
9 cardiovascular benefit; in other words, a 10:01:39
10 cardiovascular outcome trial that was positive, 10:01:41
11 yeah. 10:01:42

12 Q And the three GLP-1 receptor agonists 10:01:43
13 that had proven cardiovascular benefit were 10:01:46
14 semaglutide, liraglutide, and dulaglutide? 10:01:49

15 MR. REICH: Objection. 10:01:53

16 A Yes. 10:01:53

17 Q And the guidelines also recommend SGL-2 10:01:54
18 inhibitors for patients with type 2 diabetes and 10:01:58
19 cardiovascular disease or are at risk for 10:02:03
20 cardiovascular disease. 10:02:05

21 Is that right? 10:02:06

22 A There's nuance to these guidelines. It 10:02:06

1 talks about particular patients, to think about when
2 you'd use a particular class of drugs, for example.

3 But if we go down, you know, to
4 glucose-lowering treatment section, based on the
5 results of the cardiovascular outcome trials of
6 those studies and those drugs, yeah, there's also a
7 recommendation to consider SGL-2 inhibitors with
8 proven cardiovascular benefit in patients that are
9 high risk or very high risk with established ASCVD.

10 Q So page 10 doesn't identify a specific
11 dose of semaglutide that should be used, does it?

12 A Correct. This is a high-level summary of
13 the recommendations here. And it just lists general
14 recommendations for -- the spirit here is it's
15 saying use drugs with proven cardiovascular benefit
16 in patients that are high, very high, or with
17 existing cardiovascular disease and have type 2
18 diabetes.

19 And like many guidelines, it doesn't try
20 to make -- it's not meant to be making specific dose
21 recommendations. It talks about the chemical name
22 of these drugs.

1	MR. WHITE: We've been going for an hour.	10:03:41
2	Should we take a quick break?	10:03:43
3	MR. REICH: Sure.	10:03:44
4	(Recess from 10:03 a.m. until 10:19 a.m.)	10:12:50
5	(Previously marked Exhibits 2091 and 2092	10:19:05
6	attached to the transcript.)	10:18:21
7	BY MR. WHITE:	10:18:21
8	Q So I've handed you what's been previously	10:19:01
9	marked as Exhibit 2091 and 2092.	10:19:03
10	And do you recognize these as the	10:19:08
11	American College of Cardiology guidelines that you	10:19:10
12	reference in your declaration?	10:19:13
13	A Yes, these are the so-called expert	10:19:16
14	consensus decision pathways.	10:19:19
15	Q So in paragraph 48, you reference	10:19:43
16	Exhibit 2091. You cite to page 11.	10:19:59
17	So on page 11, is there any specific dose	10:20:07
18	of semaglutide that is being discussed there?	10:20:10
19	MR. REICH: Objection to form.	10:20:16
20	A So this is the so-called 2018 Expert	10:20:17
21	Consensus Decision Pathway, mind you, for	10:20:22
22	cardiologists, by a cardiology society, for treating	10:20:26

1 type 2 diabetes. So this is a really big paradigm
2 change in the field where we have cardiologists
3 writing about diabetes and cardiovascular disease,
4 which is kind of remarkable.

5 So these expert consensus decision
6 pathways are supposed to be sort of, as it says,
7 consensus decision pathways towards treatment.
8 They're not, strictly speaking, guidelines.

9 So they don't make proscriptive, you
10 know, mandates, what you need to do for treatment,
11 but they're supposed to guide you or direct you
12 towards where the field is headed and where patients
13 might benefit, and as such, the layout, the data,
14 and the options for lowering cardiovascular events
15 in patients with type 2 diabetes.

16 This mentions -- talking about the GLP-1
17 receptor agonists and the observations from the
18 clinical trials.

19 So on this particular page, once again,
20 they're just kind of talking about the trials. They
21 talk about the SUSTAIN-6 trial, which we've talked
22 about.

1 SUSTAIN-6, which, you know, after you 10:21:35
2 look at a document like this, you know, the 10:21:38
3 interested physician who is in this field would then 10:21:43
4 read SUSTAIN-6 and digest that in the context of 10:21:45
5 this pathway, would go back and read the SUSTAIN-6 10:21:48
6 trial and recognize the trial protocol, as we talked 10:21:51
7 about, called for a dose titration up to the target 10:21:54
8 1.0 dose subcutaneous weekly where these results 10:21:59
9 were observed, the 26 percent reduction in MACE, for 10:22:06
10 example, which is mentioned here. 10:22:11

11 So to answer your question, this 10:22:13
12 particular sets of paragraphs that are just 10:22:16
13 summarizing the trials do not go through all aspects 10:22:19
14 of the clinical trial protocol. They cite the 10:22:22
15 SUSTAIN-6 trial, for example, which would have all 10:22:26
16 the details about the dosing and things. 10:22:28

17 Q So if you look at page 14 of 10:23:06
18 Exhibit 2091. 10:23:13

19 A Yes. 10:23:15

20 Q So it's the -- I want to talk about the 10:23:18
21 first full paragraph that begins, Because type 2 10:23:22
22 diabetes is common. 10:23:25

1	A	Mm-hmm.	10:23:26
2	Q	And so six lines from the bottom of that	10:23:26
3		paragraph, or seven lines, there's a sentence that	10:23:33
4		begins, Among the GLP-1RAs with demonstrated CV	10:23:37
5		benefit, the most convincing data for CV benefit are	10:23:42
6		for liraglutide, which should currently be the	10:23:45
7		preferred member of this class for CV event	10:23:50
8		reduction, and it goes on.	10:23:52
9		Do you see that?	10:23:53
10	A	Yes.	10:23:53
11	Q	And do you agree with that statement?	10:23:54
12	A	I don't agree with that statement. I	10:23:58
13		mean, the word "most convincing," I guess, is open	10:24:03
14		for interpretation. It says, Amongst the GLP-1	10:24:06
15		receptor agonists with demonstrated benefit, the	10:24:09
16		most convincing data for cardiovascular benefit are	10:24:12
17		with lira.	10:24:14
18		I disagree. I mean, once again, we've	10:24:16
19		talked before about how it's open for interpretation	10:24:19
20		when you look across trials.	10:24:22
21		I think that -- and, you know, we've	10:24:25
22		talked about the SUSTAIN-6 trial, which showed the	10:24:28

1 26 percent reduction in major adverse cardiovascular
2 events and, for example, the LEADER trial, which
3 showed a 13 percent reduction in major adverse
4 cardiovascular events.

5 Open for interpretation.

6 I consider the 26 percent reduction in
7 cardiovascular events with a weekly injection to be
8 more convincing -- or I would use the term more
9 clinically relevant or more clinically powerful than
10 the 13 percent reduction with a daily injection of
11 lira.

12 Q So I'll look at 2092 now.

13 So you cite pages 11 and 16 of
14 Exhibit 2092. So I want to make sure we're looking
15 at the right thing in Exhibit 2092.

16 So you cite page 11 for the
17 proposition -- to support the sentence that begins,
18 In 2020, the ACC updated their expert consensus
19 decision pathway, and it goes on.

20 Do you see that sentence?

21 A Yes.

22 Q What were you pointing to on page 11 that

1 supports that proposition? 10:25:57

2 A Let me dive back into this expert 10:26:02

3 consensus decision pathway and remember the page 10:26:07

4 numbers. 10:26:11

5 So going back to read that sentence real 10:26:21

6 quick, yeah, as you said, dulaglutide, liraglutide, 10:26:23

7 and injectable semaglutide as the currently 10:26:32

8 preferred agents. 10:26:35

9 So on page 11, that's marked page 11 10:26:35

10 here, I see a discussion of SGL-2 inhibitors. So I 10:26:42

11 don't see that statement here. 10:26:48

12 Now, on the following page 12, we get 10:26:50

13 into the GLP-1 receptor agonists. So I'm not -- I 10:26:53

14 don't recall if I've reviewed a different version or 10:26:55

15 something that had different paging. But I presume 10:27:01

16 that the statement is better represented by the 10:27:04

17 GLP-1 section of this document. 10:27:08

18 Q And so as of when this guidance was 10:27:10

19 published that's 2092 -- the pathway, not 10:27:15

20 guidance -- dulaglutide, liraglutide, and injectable 10:27:19

21 semaglutide were all what were recommended as the 10:27:24

22 preferred GLP-1 receptor agonists. 10:27:27

1 Is that correct? 10:27:30

2 A Yeah, so what these guidelines or pathway 10:27:30

3 would generally do is lay out the data and say which 10:27:33

4 agents have -- the term would be established 10:27:36

5 cardiovascular benefit. And they would say, we 10:27:39

6 prefer to use -- it should be prefer to use an agent 10:27:42

7 with established cardiovascular benefit. 10:27:45

8 So this is saying, for example, that 10:27:47

9 dulaglutide, liraglutide, and injectable semaglutide 10:27:50

10 have proven cardiovascular benefit. 10:27:52

11 So it lists those as options for reducing 10:27:54

12 cardiovascular events. 10:27:58

13 Q So at the end of paragraph 48, you cite 10:29:08

14 page 14 for the proposition that the guidelines 10:29:12

15 specifically recommend the 1 milligram dose for 10:29:18

16 cardiovascular benefit when semaglutide is 10:29:23

17 administered once weekly. 10:29:27

18 So can you tell me what you were pointing 10:29:28

19 to on page 14 for that proposition? 10:29:30

20 A Sure. I'm turning to page 14 now. 10:29:32

21 I believe what I'm referring to here is, 10:29:39

22 it talks about -- for example, in 5.2.6 of the 10:29:43

1 document, it says, you know, details about the GLP-1
2 receptor agonists are in Table 4. And then if we
3 were to look at Table 4, I believe, if I recall, is,
4 yeah, the information about the GLP-1 receptor
5 agonists, and it says --

6 Q What page are you on for Table 4?

7 A Page 44 of the document. It's at the
8 end.

9 It says, Recommended doses for
10 cardiovascular benefit. And it says for semaglutide
11 subcutaneous, Titrate slowly to 1 milligram once
12 weekly or maximally tolerated. If not fully
13 tolerated at a lower dose, but titrate to the target
14 dose of 1 milligram subcutaneous once weekly,
15 consistent with the data from the trial.

16 Q And so these guidelines, they don't
17 recommend a specific GLP-1 receptor agonist,
18 correct?

19 MR. REICH: Objection to form.

20 A Yeah. The purpose of guidelines -- or in
21 this case, not even guidelines, expert consensus
22 decision pathway, that's what it's called -- is to

1 direct clinicians to the pertinent data, in this 10:31:17
2 case, in cardiovascular disease and diabetes, and 10:31:21
3 summarize the data and point to where there's 10:31:23
4 cardiovascular benefit. 10:31:26

5 It summarizes the agents with proven 10:31:29
6 cardiovascular benefit are lira, dulaglutide, as we 10:31:32
7 talked about, or subcutaneous semaglutide. 10:31:36

8 These guidelines, like most medical 10:31:40
9 guidelines, don't say, you must use this agent at 10:31:43
10 this dose. That's not what they do. They present 10:31:47
11 the options for -- in this case, since it's a 10:31:51
12 cardiovascular document -- for lowering 10:31:53
13 cardiovascular risk. 10:31:55

14 So it's consistent with the Institute of 10:31:56
15 Medicine's kind of general recommendation for how to 10:32:01
16 write guidelines, which is present the evidence, 10:32:05
17 present the options. And it's not in their purview 10:32:08
18 to tell you what to do. It's to lead you to the 10:32:10
19 data. 10:32:13

20 (Previously marked Exhibit 2087 attached 10:32:13
21 to the transcript.) 10:32:25

22 BY MR. WHITE: 10:32:25

1 Q So I've given you a copy of what's been 10:32:32
2 marked as Exhibit 2087. 10:32:34

3 Do you recognize this as the American 10:32:37
4 Diabetes Association standard of care document that 10:32:40
5 you discuss in your declaration? 10:32:43

6 A Yes. This is the 2022 version of this 10:32:45
7 ADA Standards of Medical Care. 10:32:50

8 Q So you cite to page 14. So are you 10:33:00
9 referring to the recommendations that are in the 10:33:06
10 purple box on the right-hand side? 10:33:11

11 MR. REICH: Objection to form. 10:33:14

12 A Let me just read sort of what we wrote 10:33:15
13 here -- what I wrote here, what we're talking about 10:33:17
14 here, in section 49. 10:33:21

15 It says, The American Diabetes 10:33:23
16 Association releases updated guidelines every year, 10:33:25
17 specifically covering cardiovascular disease and 10:33:29
18 risk management in type 2 diabetes. While long 10:33:31
19 recommending GLP-1 receptor agonists in general and 10:33:36
20 semaglutide in particular, the 2022 version 10:33:40
21 recommended semaglutide amongst other GLP-1 receptor 10:33:42
22 agonists with demonstrated cardiovascular disease 10:33:46

1 benefit as part of the first line treatment for 10:33:49
2 patients with type 2 diabetes with increased 10:33:52
3 cardiovascular risk to reduce the risk of major 10:33:54
4 adverse cardiovascular events before the use of 10:33:56
5 metformin and independent of the hemoglobin A1C. 10:33:59

6 So on page 14 here, as you mentioned, in 10:34:05
7 the bold -- or not in the bold, but in the colored 10:34:09
8 sections of these recommendations -- which come up 10:34:12
9 several times throughout the document, actually. 10:34:17

10 Yeah. So -- and I read what I wrote here, which is 10:34:23
11 semaglutide subcutaneous in the context of other 10:34:29
12 GLP-1 receptor agonists would demonstrate a benefit. 10:34:31

13 Yeah. And here it says, for example, in 10:34:36
14 10.42b, In patients with type 2 diabetes and 10:34:41
15 established atherosclerotic cardiovascular 10:34:49
16 disease or multiple risk factors for atherosclerotic 10:34:51
17 cardiovascular disease, a glucagon-like peptide 1 10:34:54
18 receptor agonist, a GLP-1 receptor agonist, with 10:34:57
19 demonstrated cardiovascular benefit is recommended 10:34:59
20 to reduce the risk of major adverse cardiovascular 10:35:01
21 events. 10:35:04

22 Other parts of the document would 10:35:05

1 summarize what it means by proven cardiovascular 10:35:07

2 benefit, like we've talked about. 10:35:09

3 So yeah, I think my summary here is very 10:35:11

4 well reflected here in the recommendations. 10:35:15

5 Q And so the GLP-1 receptor agonists with a 10:35:17

6 proven cardiovascular benefit are the ones that are 10:35:22

7 in Table 10.3B. 10:35:24

8 Is that right? 10:35:27

9 A Table 10.3B, yeah, is a list of trials, 10:35:35

10 actually. So 10.3B is useful, but it's actually a 10:35:42

11 list of clinical trials. It's not, you know, the 10:35:47

12 list of therapies, but it's a list of clinical 10:35:50

13 trials that were these cardiovascular safety trials 10:35:54

14 that we've talked about, and it summarizes the 10:35:56

15 results of those. 10:35:59

16 And you could see, I guess, if one were 10:36:00

17 to dive in and look at the results, and sort of 10:36:02

18 summarized this before, that the SUSTAIN-6 trial on 10:36:06

19 the primary outcome, which is at the bottom, of 10:36:10

20 three-point MACE demonstrated a 26 percent 10:36:13

21 reduction. That was with semaglutide subcutaneous 10:36:15

22 1 milligram weekly at 26 percent reduction in 10:36:18

1 three-point MACE. So obviously, that has proven
2 cardiovascular benefit.

3 LEADER, which we've talked about, showed
4 a 13 percent reduction in the three-point MACE
5 outcome consistent with a cardiovascular benefit.

6 And the REWIND trial with dulaglutide,
7 the other one that's listed, showed a statistically
8 significant 12 percent reduction in three-point
9 MACE.

10 So I think to answer your question, it
11 gets at the agents with cardiovascular benefit, but
12 it's not a list of therapies, it's a list of trials
13 and the results.

14 Q Did the ELIXA trial that's in 10.3B show
15 a proven cardiovascular benefit?

16 A That's a good question. So the ELIXA
17 trial is with lixisenatide, a different GLP-1
18 receptor agonist. So this is -- inherent in this
19 table is the idea that there's not a class effect,
20 that you have to look at the evidence to figure out
21 what leads to cardiovascular benefit.

22 And in the ELIXA trial with lixisenatide,

1 there was not a benefit on MACE outcomes. You can
2 see here, the point estimate was 1.02. The
3 confidence interval straddles 1, which means it's
4 not statistically significant, which means that
5 there's no cardiovascular benefit. There's no harm,
6 but there's no benefit.

7 Q Did exenatide in the EXSCEL trial have a
8 proven cardiovascular benefit?

9 A The EXSCEL trial, as shown here, is an
10 interesting one that used long-acting exenatide.
11 And if you were to go down to the primary outcome,
12 the point estimate was 0.91 with a confidence
13 interval that included 1 or unity, and this did not
14 produce -- it was not consistent with a
15 statistically significant reduction in
16 cardiovascular events.

17 So correct.

18 Q And so when the recommendation of that is
19 on page 14 recommends GLP-1 receptor agonists with
20 proven -- I'm sorry -- with demonstrated
21 cardiovascular disease benefit, what GLP-1 receptor
22 agonist is it referring to?

1 A What it's referring to here are the, you 10:38:29
2 know, the trials that showed cardiovascular benefit. 10:38:34
3 So that would be subcutaneous semaglutide, 10:38:37
4 liraglutide, and dulaglutide, very similar to what 10:38:43
5 we talked about earlier in the discussion. 10:38:49
6 Q And the recommendation -- there's also a 10:38:52
7 recommendation that you can use sodium-glucose 10:38:56
8 cotransporter 2, correct? 10:39:02
9 A Yes. This was very similar to the ACC 10:39:02
10 recommendations. As you can see, there's a 10:39:05
11 convergence after this paradigm shift towards these 10:39:07
12 recommendations. 10:39:11
13 So separately, yeah, there's a 10:39:11
14 recommendation for so-called SGL2 inhibitors with 10:39:13
15 proven cardiovascular benefit, not at issue here, 10:39:17
16 but for consideration in patients with type 2 10:39:20
17 diabetes with high cardiovascular risk, yes. 10:39:25
18 Q I want to look back at your declaration, 10:39:29
19 kind of more towards the beginning in paragraph 8. 10:40:06
20 A Yes. 10:40:15
21 Q And there, you mention that you were 10:40:17
22 involved with the relabeling of Victoza and the 10:40:19

1	approval of Ozempic.	10:40:24
2	A Mm-hmm.	10:40:26
3	Q So what was your involvement with the	10:40:26
4	relabeling of Victoza?	10:40:28
5	MR. REICH: Objection to form.	10:40:31
6	A Yeah, I've mentioned here that I'm what's	10:40:32
7	called a special government employee, SGE, on -- in	10:40:36
8	CDER for -- a voting member at the time -- of the	10:40:42
9	Endocrinologic and Metabolic Drug Advisory	10:40:42
10	Committee -- and actually, there's a typo, it should	10:40:56
11	be EMDAC -- which is an advisory committee that's	10:40:59
12	convened when, you know, the FDA requires input from	10:41:02
13	experts or clinicians in the field.	10:41:07
14	And I was a voting member, which means I	10:41:09
15	was on the committee for consideration of these	10:41:13
16	issues at hand. So -- and I was on the advisory	10:41:18
17	committee, as it says here, many things, including	10:41:22
18	the approval of Repatha, that's a	10:41:24
19	cholesterol-lowering drug; the relabeling of	10:41:28
20	so-called Victoza, lira, which was on the market,	10:41:31
21	but then, after the safety data or, of course, the	10:41:33
22	benefit from the LEADER trial became apparent, was	10:41:37

1 up for relabeling, so there was a discussion there; 10:41:40
2 the approval of Ozempic, of course, Ozempic being, 10:41:42
3 you know, target 1 milligram subcutaneous weekly of 10:41:48
4 semaglutide, and so forth. 10:41:50

5 So I was on the advisory committee, 10:41:52
6 so-called ADCOM, for discussion of these, yes. 10:41:56

7 Q So what's the role of the advisory 10:41:59
8 committee? 10:42:02

9 MR. REICH: Objection to form and scope. 10:42:02

10 A The role of the advisory committee is 10:42:06
11 just that, it's to provide advisory to the FDA for 10:42:08
12 these matters. 10:42:13

13 Q So in paragraph 6 you reference you 10:42:16
14 received a grant from Novo Nordisk. 10:42:20

15 A Yes. 10:42:24

16 Q Do you recall what that grant was for? 10:42:26

17 A Yeah, so this grant is an educational 10:42:27
18 grant to my institution, and this grant was, I 10:42:30
19 believe, for \$55,000 over the course of one year. 10:42:36

20 This was an educational grant to support 10:42:41
21 our teaching, because we have a class on -- it's a 10:42:44
22 week-long course on cardiac computed tomography, CT. 10:42:49

1 And given the changing field, we have now 10:42:55
2 incorporated elements of teaching about diabetes in 10:42:58
3 particular in the course. 10:43:00

4 And the educational grant from Novo 10:43:01
5 Nordisk went to my institution for this CME course, 10:43:06
6 continuing medical education course, supported the 10:43:07
7 conversation about cardiovascular risk and diabetes 10:43:10
8 and obesity. 10:43:13

9 Q Is that the only grant you received from 10:43:14
10 Novo Nordisk? 10:43:18

11 A Yeah. Once again, that was to my 10:43:19
12 institution. But that's the only grant from Novo 10:43:21
13 Nordisk to my institution or me that we received, 10:43:23
14 correct. 10:43:28

15 Q Other than that grant and your work on 10:43:29
16 this case, have you received any other fees from 10:43:31
17 Novo Nordisk? 10:43:33

18 A Yeah, I've -- subsequent to the FDA 10:43:35
19 experience, I've consulted with Novo Nordisk several 10:43:39
20 times in an advisory capacity. That's, I think, 10:43:42
21 detailed here. 10:43:48

22 Q And are those paid positions? 10:43:54

1	A	It's not a position. Yeah, for your time	10:43:56
2		consulting, you get remunerated, yeah.	10:43:59
3	MR. WHITE:	I have nothing further.	10:44:04
4	MR. REICH:	We'll take a few-minute	10:44:06
5		break.	10:44:08
6		(Recess from 10:44 a.m. until 11:08 a.m.)	11:07:59
7		EXAMINATION	11:08:01
8	BY MR. REICH:		11:08:01
9	Q	Dr. Blaha, earlier you were asked about	11:08:06
10		paragraph 48 and certain citations to Exhibit 2092.	11:08:10
11		Do you recall those?	11:08:15
12	A	Yeah.	11:08:22
13	Q	So if you could turn to paragraph 48 of	11:08:22
14		your report, please -- your declaration.	11:08:25
15	A	Okay.	11:08:36
16	Q	If you could also pull up Exhibit 2092,	11:08:37
17		which is the 2020 Expert Consensus Decision Pathway.	11:08:42
18	A	Got it.	11:08:45
19	Q	And in the middle of paragraph 48,	11:08:46
20		there's the sentence that says, In 2020, the ACC	11:08:52
21		updated their Expert Consensus Decision Pathway on	11:08:56
22		novel therapies for cardiovascular risk reduction in	11:08:59

1	patients with type 2 diabetes recommending	11:09:03
2	dulaglutide, liraglutide, and injectable semaglutide	11:09:05
3	as the currently prefers agents.	11:09:09
4	Do you see that?	11:09:13
5	A Mm-hmm.	11:09:13
6	Q And there's a citation to page 11?	11:09:14
7	A Yes.	11:09:16
8	Q And if you turn to page 12 of	11:09:16
9	Exhibit 2092, let me know when you're there.	11:09:19
10	A Okay, page 12.	11:09:21
11	Q Do you see that sentence in the second	11:09:24
12	full paragraph under section 5.2?	11:09:27
13	A Yes.	11:09:41
14	Q Did you intend to cite page 12 and not	11:09:43
15	page 11?	11:09:46
16	A Yes. This is the sentence.	11:09:46
17	Q Similarly, the next sentence -- two	11:09:49
18	sentences later in paragraph 48, there's a quote	11:09:51
19	that says, but that there is a potential for	11:09:53
20	clinically relevant heterogeneity within the class,	11:09:56
21	and it cites to page 11 of Exhibit 2092.	11:09:59
22	Do you see that?	11:10:02

1	A	Point me to the sentence again.	11:10:05
2	Q	In paragraph 48 of your declaration.	11:10:07
3	A	Okay, yeah.	11:10:09
4	Q	Two sentences later, there's a quote, and	11:10:10
5		it says that there is a potentially for clinically	11:10:12
6		relevant heterogeneity.	11:10:15
7	A	Yes, I see that phrase.	11:10:16
8	Q	And if you go to the same paragraph on	11:10:18
9		page 12 of Exhibit 2092, do you see that sentence --	11:10:21
10	A	Yes.	11:10:24
11	Q	-- that quote?	11:10:25
12	A	I see that quote, yeah.	11:10:25
13	Q	Did you intend to cite to page 12?	11:10:27
14	A	Yes.	11:10:29
15	Q	And earlier, you were also asked	11:10:30
16		questions by Mr. White about comparing the LEADER	11:10:33
17		and SUSTAIN trials.	11:10:36
18		Do you recall those questions?	11:10:38
19	A	Yes.	11:10:39
20	Q	What was the reaction among cardiologists	11:10:39
21		to the LEADER study which administered liraglutide	11:10:44
22		once daily to patients with type 2 diabetes?	11:10:48

1	MR. WHITE: Objection, scope, beyond the	11:10:50
2	cross.	11:10:53
3	A What I remember at the time is the	11:10:54
4	skepticism of -- in light of what we talked about,	11:10:59
5	in light of the absence of data for cardiovascular	11:11:04
6	benefit, when the results came out, there was	11:11:08
7	skepticism because of the small effect size and the	11:11:11
8	results. There was sort of muted response, sort of	11:11:17
9	like a skeptical response to those results.	11:11:21
10	Q And did cardiologists respond differently	11:11:29
11	to the SUSTAIN data?	11:11:32
12	A Yes.	11:11:34
13	MR. WHITE: Objection.	11:11:34
14	Q And how so?	11:11:36
15	MR. WHITE: Objection.	11:11:37
16	A I would say SUSTAIN-6 data, which showed	11:11:37
17	the 26 percent reduction in major adverse	11:11:44
18	cardiovascular events, which is a large reduction,	11:11:47
19	more like what we see with other cardiovascular	11:11:50
20	drugs, for example, and then there was also a	11:11:52
21	39 percent reduction in stroke, which is a	11:11:57
22	cardiovascular outcome, with a weekly injection.	11:12:00

1 I think there was a lot of excitement, 11:12:05
2 and I think it was considered practice-changing, 11:12:08
3 paradigm-changing at the time to have a drug that 11:12:12
4 has such large -- once again, 26 percent or 11:12:15
5 39 percent for stroke -- cardiovascular benefit with 11:12:18
6 the weekly injection. 11:12:21

7 So I think it was practice-changing, 11:12:22
8 paradigm-changing, whatever, yeah. 11:12:25

9 Q Is there a particular dose in the 11:12:29
10 SUSTAIN-6 trial that you think -- that in your 11:12:31
11 opinion led to these better outcomes? 11:12:36

12 MR. WHITE: Objection. 11:12:39

13 A We talked before about how -- you know, 11:12:41
14 results in the dosing, and I -- the result -- the 11:12:45
15 most impressive results for cardiovascular risk 11:12:49
16 reduction in the SUSTAIN-6 study were with the 11:12:52
17 1 milligram subcutaneous weekly dose of semaglutide, 11:12:55
18 I think as we talked about before. 11:12:58

19 So I think, in answering your question, 11:13:01
20 I'd say the 1 milligram dose is the most impressive 11:13:04
21 results in cardiovascular risk reduction, 11:13:07
22 subcutaneous weekly, that dose. 11:13:11

1 Q And is this what you referred to as the 11:13:13
2 paradigm shift in your declaration? 11:13:15

3 MR. WHITE: Objection. 11:13:18

4 A Yeah, what I referred to as the paradigm 11:13:19
5 shift was just the clinical paradigm shift of people 11:13:22
6 thinking differently, cardiologists specifically 11:13:25
7 thinking differently about managing cardiovascular 11:13:28
8 risk in diabetes. 11:13:32

9 The results of -- for example, the 26 11:13:32
10 percent reduction or the 39 percent reduction in 11:13:35
11 stroke led to a practice change, a thinking change 11:13:38
12 about how we're going to manage those patients 11:13:42
13 that's reflected, I think, after that in guidelines 11:13:44
14 and pathway documents, et cetera. It was 11:13:46
15 practice-changing. So yeah, the paradigm change is 11:13:48
16 a thinking change about how we manage patients in 11:13:52
17 practice, is the way I refer to it. 11:13:55

18 Q What GLP-1 agonist do you primarily use 11:13:56
19 to treat patients with type 2 diabetes that are also 11:14:00
20 at risk for cardiovascular events? 11:14:02

21 MR. WHITE: Objection. 11:14:04

22 A Yeah, in my cardiometabolic clinic, which 11:14:06

1 is full of patients with diabetes and high 11:14:12
 2 cardiovascular risk, I prefer to use Ozempic, which 11:14:15
 3 is semaglutide, subcutaneous semaglutide once 11:14:19
 4 weekly, for its cardiovascular benefits. So 11:14:24
 5 targeting the 1 milligram dose. I think I said 11:14:29
 6 that. 11:14:32

7 So yeah, that's the one I use. That's my 11:14:33
 8 go-to agent for these patients based on these data, 11:14:35
 9 the data we've talked about. 11:14:39

10 Q In your opinion, is that consistent with 11:14:40
 11 other cardiologists in the field, their practice? 11:14:42

12 MR. WHITE: Objection. 11:14:44

13 A Yeah. I would say, yeah, definitely, 11:14:45
 14 that this is very consistent with practice patterns 11:14:49
 15 in people that manage cardiovascular disease and 11:14:52
 16 diabetes around the country, that people use Ozempic 11:14:55
 17 for cardiovascular risk reduction as the preferred 11:15:00
 18 agent with the goal of titrating to the 1 milligram 11:15:05
 19 clinical trial dose. 11:15:09

20 Q Earlier, you were asked questions about 11:15:17
 21 semaglutide versus other GLP-1 agonists. 11:15:21

22 Do you recall those questions? 11:15:24

1	A	Yeah, yes.	11:15:25
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2	Q And as between Ozempic and liraglutide,	11:15:28
3	were the results from the SUSTAIN-6 study surprising	11:15:35
4	to you?	11:15:38

5	A	Yes.	11:15:38
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6	MR. WHITE: Objection.	11:15:39
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7	A	Yeah, definitely. When, you know, this	11:15:40
8		paper came out, it was very surprising to see the	11:15:43
9		magnitude of benefit on major adverse cardiovascular	11:15:48
10		events that was observed here, particularly stroke,	11:15:51
11		in light of a weekly injection, you know, less	11:15:55
12		frequent dosing of a therapeutic.	11:15:59

13	So yeah, it was surprising, exciting,	11:16:01
14	practice-changing, paradigm-shifting, incredible.	11:16:06
15	Yes. I think that answers your question.	11:16:16

16	Q And were those SUSTAIN-6 data surprising	11:16:18
17	in view of the results for Bydureon?	11:16:21

18	MR. WHITE: Objection.	11:16:25
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19	A	Yeah. Yeah. Absolutely. It's	11:16:26
20		absolutely, you know, super exciting and unexpected	11:16:32
21		compared to other therapies that didn't show the	11:16:36
22		same benefit -- degree of benefit or benefit on	11:16:39

1 cardiovascular outcomes. So absolutely. 11:16:42

2 Q And were those SUSTAIN-6 data surprising 11:16:45
3 in view of the results for dulaglutide? 11:16:47

4 MR. WHITE: Objection. 11:16:49

5 A Likewise, I think, yeah, once again, 11:16:51
6 weekly injection, 26 percent benefit on MACE 11:16:55
7 outcomes, which I think is clear is clinically 11:17:01
8 relevant reduction in adverse cardiovascular events. 11:17:06

9 There's a 39 percent of stroke that was 11:17:10
10 extremely unique for SUSTAIN-6, too. So I found it 11:17:14
11 extremely surprising, unexpected compared to the 11:17:18
12 small benefit observed in the REWIND trial, which 11:17:24
13 was dulaglutide. 11:17:29

14 Q Were there any other therapies for type 2 11:17:36
15 diabetes that provided the cardiovascular benefits 11:17:41
16 similar to Ozempic that existed as of 2012? 11:17:45

17 MR. WHITE: Objection. 11:17:49

18 A Definitely not. As of 2012 -- I mean, I 11:17:50
19 detailed in my report, as of 2012, there was great 11:17:54
20 skepticism of the idea of lowering glucose 11:17:59
21 aggressively with lower cardiovascular events. 11:18:01

22 The thinking in the field was, including 11:18:05

1 myself, was that there might even be an increased 11:18:08
2 risk of cardiovascular disease at that time. 11:18:11

3 So it was extremely surprising, in light 11:18:13
4 of that, I guess, that we see such incredible 11:18:15
5 cardiovascular benefits with the SUSTAIN-6 trial. 11:18:18

6 MR. REICH: I have no further questions. 11:18:20

7 MR. WHITE: I have nothing further, but I 11:18:23
8 just note our objection for the record, the last set 11:18:25
9 of questions were beyond the scope of the 11:18:28
10 cross-examination and attempted to elicit new 11:18:31
11 testimony that is outside the scope of the report. 11:18:35
12 We object to that, and we reserve our right to move 11:18:37
13 to exclude that testimony. 11:18:40

14 MR. REICH: We disagree. We note your 11:18:42
15 objection. 11:18:45

16 COURT REPORTER: Anything else for the 11:18:46
17 record? 11:18:47

18 MR. WHITE: Nothing from me. 11:18:49

19 (Transcript orders discussed.) 11:18:50

20 COURT REPORTER: Thank you. That's all I 11:19:48
21 need. 11:19:49

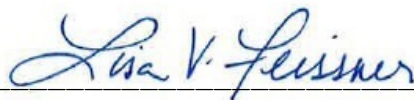
22 (Off the record at 11:19 a.m.)

C E R T I F I C A T E

I, Lisa V. Feissner, RDR, CRR, CLR, do
hereby certify that the witness was first duly sworn
by me and that I was authorized to and did report
said proceedings.

I further certify that the foregoing
transcript is a true and correct record of the
proceedings; that said proceedings were taken by me
stenographically and thereafter reduced to
typewriting under my supervision; that reading and
signing was not requested; and that I am neither
attorney nor counsel for, nor related to or employed
by, any of the parties to the action in which this
deposition was taken; and that I have no interest,
financial or otherwise, in this case.

IN WITNESS WHEREOF, I have hereunto set
my hand this 16th day of APRIL, 2024.



Lisa V. Feissner, RDR, CRR, CLR

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