

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2
3 BEFORE THE PATENT TRIAL AND APPEAL BOARD

4
5 MYLAN PHARMACEUTICALS, INC.,

6 Petitioners,

7 v.

8 NOVO NORDISK A/S,

9 Patent Owner.

10
11 Case IPR2023-00724

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

13
14 Deposition of STEVEN COCA, D.O., M.D.

15 Conducted Virtually

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22 Reported by: Judith E. Bellinger, RPR, CRR

1 Deposition of STEVEN COCA, D.O., M.D.,
2 conducted virtually.

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11 Pursuant to notice, before Judith E.
12 Bellinger, Registered Professional Reporter,
13 Certified Realtime Reporter, and Notary Public in
14 and for the State of Maryland.

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1 P R O C E E D I N G S

2 STEVEN COCA, D.O., M.D.,

3 Being first duly sworn, was examined
4 and testified as follows:

5 EXAMINATION BY COUNSEL FOR THE PATENT OWNER

6 BY MR. REICH:

7 Q Good morning, Dr. Coca.

8 A Good morning, Josh.

9 Q How are you today?

10 A Doing well. How are you?

11 Q Not bad.

12 Have you ever been deposed before?

13 A Yes, I have.

14 Q And when was that deposition?

15 A Late 2023.

16 Q And what was the subject matter of that
17 deposition?

18 A Subject matter was related to proton
19 pump inhibitors and their association with chronic
20 kidney disease.

21 Q And was it a patent case or was it a
22 different proceeding?

1 A It was not a patent case.

2 Q And do you remember who the parties
3 were?

4 A I was testifying on behalf of Takeda
5 Pharmaceuticals.

6 Q And the subject matter of your
7 testimony, what did it relate to, specifically?

8 A It was related to the question of
9 whether proton pump inhibitors were causative for
10 the development of chronic kidney disease, and
11 there was a generic report that I did, and there
12 were case-specific reports in related depositions.

13 Q Have you been deposed in any other
14 matters?

15 A No.

16 Q So I'm sure you're aware of some of the
17 basics from your prior deposition, but just want
18 to cover a few items.

19 First, it's important that we don't
20 talk over each other, we have a court reporter
21 and, for a clear record, it's important that I ask
22 a question, I pause, I give you a chance to

1 answer, and then rinse and repeat.

2 Do you understand that?

3 A I understand.

4 Q Second, please provide verbal answers,
5 you know, nods and shakes won't be picked up.

6 It's very natural to do. So to the best of your
7 ability, please, try and remember to say yes or
8 no, and if not, I'll try and remind you.

9 Fair?

10 A Will do.

11 Q And I'll try my best to ask clear
12 questions. If at any point you don't understand a
13 question I've asked, please, ask me to rephrase
14 it. But if you don't, I'm going to assume you
15 understood the question that I've asked.

16 Is that fair?

17 A That is fair.

18 Q And what did you do to prepare for
19 today's deposition?

20 MR. ANSTAETT: Dr. Coca, I'll just
21 caution you that in answering this question, you
22 shouldn't reveal the content of any communications

1 you've had with lawyers.

2 But, otherwise, you can answer.

3 A Josh, in preparation in regards to this
4 deposition today, throughout the whole history of
5 my work on this or just immediately recent
6 activities?

7 Q Let's just be clear. What you did to
8 prepare for today's deposition.

9 A Early on, of course, there was review
10 of the patent, the relevant literature, the
11 drafting and editing of the declaration. And most
12 recently, I met with counsel to discuss -- and
13 reviewed my declaration again since it was a
14 little bit of time since it was first drafted and
15 we reviewed some of the pertinent literature and
16 exhibits associated with my declaration.

17 Q Is everything you reviewed cited in
18 your declaration or did you review anything
19 outside, that was not identified as considered in
20 your declaration?

21 A I would -- I guess one additional
22 review I did was of the recently published FLOW

1 trial in the New England Journal that was
2 potentially pertinent to this case, also, just
3 pertinent to my clinical practice and clinical
4 research that I do, since it was a groundbreaking
5 clinical trial published in the New England
6 Journal, presented at the European conference a
7 few months ago. And also, I reviewed some of the
8 references that were embedded in that FLOW trial
9 publication.

10 So that all came out after the
11 declaration.

12 Q Is the New England Journal a
13 prestigious medical journal?

14 A Yes, it is.

15 Q Fair to say one of the most prestigious
16 medical journal in the world?

17 MR. ANSTAETT: Objection. Form.

18 A It was one of the -- it has one of the
19 highest impact factors.

20 Q And I heard you say it was a
21 groundbreaking clinical trial; is that right?

22 MR. ANSTAETT: Objection. Form.

1 A Yeah. Some qualify it that way.

2 Q Could you, please, explain why some
3 qualify the FLOW trial as a groundbreaking
4 clinical trial?

5 A It was an anticipated trial because it
6 was one of the first GLP trials to study a
7 diabetic kidney disease cohort at the outset, with
8 a primary endpoint that was related to all kidney
9 events, hard kidney clinical end points.

10 Q When you say hard clinical kidney end
11 points, could you, please, explain what you mean
12 by that?

13 A Yeah, generally, and this has been
14 somewhat of a moving target in nephrology and
15 communities, but, generally, the endpoint consist
16 of a need for dialysis or end-stage -- or a
17 termination -- or a classification of end-stage
18 kidney disease with a significant -- and/or a
19 significant reduction in eGFR from baseline.
20 Typically, these trials use a predefined threshold
21 of 40 percent, 50 percent, or 57 percent decrease
22 in eGFR as part of the composite kidney endpoint.

1 Q What would not be a hard clinical
2 kidney endpoint? What are some examples?

3 A Generally, the more intermediate-type
4 end points are continuous changes in serum
5 creatinine or eGFR, or eGFR slope, changes in
6 urine albumin or urine protein, typically
7 classified as a urine-albumin-to-creatinine ratio,
8 or urine-protein-to-creatinine ratio.

9 So those are more intermediate and not
10 considered some of the hard, definitive clinical
11 end points that we use in nephrology trials.

12 Q Would change in blood pressure be
13 considered a soft endpoint?

14 A Change in blood pressure is not a hard
15 clinical endpoint, correct.

16 Q Would change in blood glucose also not
17 be a hard clinical endpoint?

18 A Correct.

19 Q And so, I think you had testified that
20 this was one of the first trials to look at a --
21 strike that.

22 So you said it was one of the first GLP

1 trials to study a diabetes disease cohort at the
2 outset, with the primary endpoint that was related
3 to all kidney end points.

4 Do you remember that?

5 A Yes.

6 Q What were the previous ones? Did you
7 discuss those in your declaration?

8 MR. ANSTAETT: Objection. Form.

9 A Yes, there have been -- yes, I
10 discussed many of the previous studies in my
11 declaration.

12 Q And those studies relate to hard
13 clinical -- hard kidney clinical end points?

14 A Some do, some don't. Some of the end
15 points, the kidney end points were secondary
16 outcomes and were -- and some were softer clinical
17 end points, and some were hard clinical outcomes
18 assessed, but not of the primary endpoint.

19 Q I think we'll circle back.

20 But just to cover some other basic
21 points.

22 Who else is in the room with you right

1 now?

2 A David and Chris.

3 Q And do you have any materials in the
4 room with you right now?

5 A Yes. I have a copy -- a paper copy of
6 my declaration and a paper copy of my CV.

7 Q Do you have any other paper copies with
8 you?

9 A No, I don't.

10 Q And are those clean copies, no notes,
11 no anything else?

12 A Correct. Clean copies.

13 Q Okay. And on the screen right now, do
14 you have anything up besides this Zoom meeting?

15 A No. Nothing besides the Zoom meeting.

16 Q Okay. Will you let me know if that
17 changes?

18 A Yes, I will.

19 Q So, you understand that you are here
20 today because you provided a declaration in IPR
21 2023-00724?

22 A Yes.

1 Q And your declaration is Exhibit 1306?

2 A Correct.

3 Q And your declaration is Exhibit 1306?

4 A Correct.

5 Q And if today I refer to that
6 Exhibit 1306 as your declaration, or your report,
7 do you understand that they're all the same thing,
8 right?

9 Exhibit 1306 is your declaration and
10 your report?

11 A Yes, I understand.

12 Q Okay. And you understand that you
13 provided opinions on behalf of Petitioner Mylan in
14 this proceeding?

15 A Yes, I do.

16 Q Okay. Did you write your declaration?

17 MR. ANSTAETT: Objection.

18 I'm going to instruct the witness not
19 the answer. That calls for privileged
20 information.

21 MR. REICH: I think I'm entitled to
22 know if he wrote any part of his declaration,

1 Dave.

2 MR. ANSTAETT: I think that gets into
3 the work product protection, Josh.

4 Q Does your declaration reflect your
5 opinions?

6 A Yes, it does.

7 Q When you were reviewing your
8 declaration, was there anything inaccurate that
9 you wanted to call to my attention today?

10 A No.

11 Q In your declaration, you describe a
12 fair amount of references, correct?

13 A Correct.

14 Q Do you think your description of those
15 references are fair?

16 A Yes.

17 Q And you have no changes that you want
18 to make today to your declaration; is that right?

19 A Correct.

20 Q You're a treating physician; is that
21 correct?

22 A Yes.

1 Q In your opinion, what does it mean to
2 treat type 2 diabetes?

3 A It's a broad question.

4 Anything specific about treatment of
5 type 2 diabetes? There's a lot of aspects to
6 that.

7 Q Is treating type 2 diabetes limited to,
8 for example, reducing HbA1c in a patient?

9 MR. ANSTAETT: Objection. Form.

10 A No. It's complicated.

11 Q In what way is it complicated?

12 A First, glycemic control is one of the
13 primary objectives in treating someone with
14 diabetes, but, first of all, there is a -- it's
15 not a complete continuum. You can't control
16 glucose excessively or you can induce the risk of
17 hypoglycemia. So it's finding the right range of
18 glucose for a given patient that's well-tolerated.

19 Generally, patients with diabetes can
20 also have hypertension and we use agents to treat
21 hypertension. There's also, obviously, dietary
22 considerations. An assessment of organs, the

1 eyes, the heart, the kidneys, the nervous system.

2 The list goes on and on.

3 So, I mean, it's a complex
4 multifactorial assessment and intervention.

5 Q So in your opinion, would treating type
6 2 diabetes encompass treating the symptoms and
7 complications that come from type 2 diabetes?

8 MR. ANSTAETT: Objection. Form.

9 A Well, it depends where the patient is
10 on their continuum of disease and whether it's
11 new-onset or long-standing diabetes, and whether
12 they have manifested any complications heretofore
13 from their diabetes. So, there's a lot to
14 consider there, on an individual basis.

15 Q So if I say "chronic kidney disease" or
16 "CKD," do you understand those to be the same
17 thing?

18 A Yes.

19 Q Would you agree that chronic kidney
20 disease can be caused by type 2 diabetes?

21 MR. ANSTAETT: Objection to form.

22 A Yes.

1 Q Would you consider chronic kidney
2 disease to be a symptom of type 2 diabetes?

3 A I would not classify it as a symptom.

4 Q What would you classify chronic kidney
5 disease as?

6 A I would classify it as a potential
7 complication of diabetes, and I'd classify it as a
8 syndrome.

9 Q So you agree that chronic kidney
10 disease is a complication of type 2 diabetes?

11 A It can be.

12 Q In your opinion, if you treat a
13 patient's -- strike that.

14 In your opinion, if a patient with type
15 2 diabetes also has chronic kidney disease, would
16 you consider treating that patient's chronic
17 kidney disease to be treating their type 2
18 diabetes?

19 MR. ANSTAETT: Objection to form.

20 A No.

21 Q You said you reviewed the patent in
22 this case, correct?

1 A Correct.

2 MR. REICH: So, Sean, if you could,
3 please, pull up Exhibit 1001.

4 (Coca Exhibit 1 marked for
5 identification and attached to the transcript.)

6 MR. ANSTAETT: Stand by, Counsel.

7 Q And, Dr. Coca, if you have a paper copy
8 of Exhibit 1001 in front of you. I understand you
9 said you didn't, but if you do and you want to
10 look at it, just let me know, that's fine with me.
11 Otherwise, I'll direct you.

12 PLANET DEPOS TECHNICIAN: Exhibit 1001
13 is up.

14 Q Can you, please, turn to column 5,
15 line 16?

16 MR. ANSTAETT: When we, or when Josh
17 brings up exhibits, can we throw those in the
18 chat, please?

19 PLANET DEPOS TECHNICIAN: Sure,
20 Counsel.

21 MR. REICH: Do you have it, Dave?

22 MR. ANSTAETT: I do not. I just happen

1 to have a paper copy of the patent, you know, with
2 me. So, you can go ahead and ask questions about
3 this, but, you know, for future exhibits, I am
4 going to want to get them in the chat. And this
5 one hasn't shown up yet.

6 PLANET DEPOS TECHNICIAN: Stand by,
7 Counsel. I'm uploading it to the chat.

8 MR. ANSTAETT: I didn't know if I had
9 to refresh the chat.

10 PLANET DEPOS TECHNICIAN: I'm just
11 going to create a OneDrive link and I'll put all
12 the exhibits in there.

13 MR. ANSTAETT: Okay.

14 PLANET DEPOS TECHNICIAN: The link is
15 up.

16 MR. ANSTAETT: I see it. I'm just
17 opening it up and, yeah, I got it. Thank you.

18 Steve, are you able to see on your
19 screen?

20 THE WITNESS: Yeah. I see the current
21 page, yeah.

22 MR. REICH: So, Sean, if we could turn

1 to column 5, I believe it's around page 9 or 10,
2 but it'll be in the top left.

3 Q Dr. Coca, do you see, starting on
4 line 16, the definition of treatment or treating
5 in the spec?

6 A Line 16? Is that with the prevention
7 and/or treatment of eating disorders?

8 Q Sorry, on the left-hand side is column
9 5. "In one embodiment the term 'treatment' or
10 'treating' as used herein means the management and
11 care of a patient for the purpose of combating a
12 condition such as disease or disorder." And then
13 it continues and it says -- sorry. "The term
14 'treatment' or 'treating' is intended to include
15 the full treatment or treatments for a given
16 condition from which the patient is suffering,
17 such as administration of the active compound to
18 alleviate the symptoms or complications."

19 Do you see that?

20 A I see that.

21 Q So with that definition in mind, would
22 you agree that treating a patient that has chronic

1 kidney disease and type 2 diabetes, that treating
2 the patient's chronic kidney disease is part of
3 treating the patient's type 2 diabetes?

4 MR. ANSTAETT: Objection to form.
5 Calls for a legal conclusion.

6 A Treating the kidney disease is not
7 considered treating the diabetes.

8 Q So you had previously agreed that
9 chronic kidney disease is a complication of type 2
10 diabetes.

11 Do you recall that?

12 A Yes. It can be.

13 Q And you agree that treating chronic
14 kidney disease is at least treating a complication
15 of the patient's type 2 diabetes?

16 MR. ANSTAETT: Objection to form.

17 A It depends on the individual patient.
18 There are patients that have chronic kidney
19 disease, in the setting of type 2 diabetes, that
20 is not necessarily due to diabetic kidney disease.
21 We've learned this from biopsy studies in patients
22 with type 2 diabetes and CKD. And depending on

1 the study, up to a quarter of patients with type 2
2 diabetes and chronic kidney disease may have a
3 different etiology of their chronic kidney
4 disease, so, it depends.

5 Q But when it's a complication of type 2
6 diabetes, you would agree treating CKD is treating
7 that complication?

8 MR. ANSTAETT: Objection to form.

9 A Well, when we say "treating CKD,"
10 heretofore, we don't have agents that necessarily
11 directly treat the kidney disease. We have agents
12 that slow -- potentially slow the progression of
13 that kidney disease. There is no -- there's not
14 necessarily a cure for this chronic kidney
15 disease.

16 Q What do you mean by "heretofore"?

17 A All treatments, so-called treatments
18 for -- well, for certain types of chronic kidney
19 disease, do not completely stop the progression,
20 as opposed to there are certain classes of
21 immune-mediated kidney disease, some of the
22 glomerulonephritis, where there are treatment

1 protocols that are instituted specifically to
2 target the kidneys and resolve the underlying
3 issue in the kidneys and return kidney function to
4 normal and alleviate that kidney damage so that
5 the patient doesn't regress.

6 So that's where I'm drawing the
7 distinction.

8 Q In 2010, was it known why chronic
9 kidney disease was caused by type 2 diabetes?

10 A Well, there were -- by 2010, there
11 were -- there were complex paradigms that were
12 known and published. Of course, science keeps
13 advancing through the years and, as a scientific
14 field, some of that has advanced. But we did know
15 that type 2 -- chronic kidney disease, in the
16 setting of diabetes, is a complex syndrome that
17 involves multiple pathways of injury to the -- to
18 various compartments in the kidney, including the
19 glomerular structures, the vasculature, the
20 tubular interstitium, and part of it involved
21 inflammation, part of it involved activation of
22 pro-fibrotic pathways, et cetera.

1 So, it has been known, for some time,
2 that it is a complex syndromic condition.

3 MR. REICH: So if we could pull up your
4 declaration, Exhibit 1306, and go to page 32,
5 paragraph 66.

6 (Coca Exhibit 2 marked for
7 identification and attached to the transcript.)

8 PLANET DEPOS TECHNICIAN: Stand by.

9 A I have that.

10 Q And in the bottom half you wrote, "The
11 exact mechanism by which hyperglycemia causes
12 chronic kidney disease is remarkably complex and
13 still poorly understood today."

14 Do you see that?

15 A I see that.

16 MR. ANSTAETT: Objection. Form.

17 Q I should have read the whole part of
18 the sentence, but in the first it says "while the
19 empirical connection between diabetes (i.e.,
20 hyperglycemia) and CKD have long been known and
21 accepted, the exact mechanism by which
22 hyperglycemia causes CKD is remarkably complex and

1 still poorly understood today."

2 Do you see that?

3 A I see that.

4 Q Do you agree with that?

5 A Yes. Because it is -- I mean, there
6 are various paradigms, as shown in this schematic
7 by Pyram, that is in the exhibit on page 33. But,
8 again, paradigms like this continue to expand,
9 continue to be modified, and the -- you know, the
10 whole answer is not completely known, again,
11 because it's complex and it also varies by
12 individual. But the point here was that it is
13 multifactorial and complex, involving multiple
14 molecular and cellular pathways that result in
15 injury to various kidney compartments and kidney
16 tissue.

17 Q Okay. But to be clear, do you agree
18 that the exact mechanism by which type 2 diabetes
19 causes chronic kidney disease is remarkably
20 complex and still poorly understood today?

21 A I agree that it's remarkably complex
22 and I agree it's not completely understood today.

1 Q Have you ever prescribed Ozempic?

2 A I, myself, have not triggered a
3 prescription for it in my practice.

4 Q What do you mean you "have not
5 triggered a prescription for it" in your practice?

6 A First of all, I'm at an academic
7 medical center where I -- we have trainees always
8 with us, both in the inpatient/outpatient
9 settings. Most of my clinical time is actually on
10 the inpatient nephrology consultative services,
11 both on the general wards and in the intensive
12 care units at the Mount Sinai Hospital.

13 My outpatient responsibilities include
14 precepting of the nephrology fellows in the CKD
15 clinic. And thus, in that supervisory role, the
16 attending, such as myself, do not -- we do not
17 enter the prescriptions, the fellows are the ones
18 entering the orders for various prescriptions of
19 any type. And those are the patients we have
20 primary or more management of. There's some
21 patients, depending on who they were referred
22 from, where we give suggestions back to the

1 primary care provider or the endocrinologist that
2 refer the patient to our clinic.

3 So that's why it was a complex answer.

4 Q So as part of this triggering or
5 precepting, do you suggest what therapy should be
6 prescribed to a particular patient?

7 A Yes.

8 Q When was the first time you suggested,
9 in this role, to prescribe Ozempic to a patient?

10 A Two things. One, we -- in general, we
11 view the recently -- we call it the
12 guideline-directed medical therapies, including
13 Ozempic, which fits in the GLP-1 receptor agonist
14 class, the SGL-2 [sic] inhibitor class, which is
15 for transcription, it's the sodium-glucose
16 cotransporter 2 inhibitor class of medications.
17 And, also, the nonsteroidal mineralocorticoid
18 receptor antagonist, specifically, in that case,
19 finerenone.

20 But for the latter two, for the GLP-1
21 and the SGLT2, we generally do not have a
22 preference in the agent when we suggest these

1 therapies to the patients or back to the referring
2 physicians. It's generally a class recommendation
3 that becomes an issue of pragmatism, in regards to
4 patient's insurance coverage, their formulary
5 coverage for which one would be the most
6 affordable.

7 So, to answer your question on timing,
8 it's been, obviously, the last couple of years the
9 GLP-1s have been in the guidelines for diabetes,
10 as well as the SGLT2 inhibitors. So, again,
11 there's not been a direct recommendation for
12 Ozempic, it would just be this patient should be
13 on these classes of medications to -- for their
14 kidney disease.

15 Q Has that view changed at all, based in
16 view of the groundbreaking New England Journal of
17 Medicine article publishing on the FLOW trial?

18 A Not that I've -- not to my knowledge,
19 and not that I've seen. It's generally still
20 known -- known, at least, again, in my view, in my
21 practice, or what I've seen at conferences. I
22 don't think people are going to switch GLP-1s

1 based on FLOW. And moreover, even though the
2 latest guidelines, whether the 2024 KDIGO
3 guidelines, that's K-D-I-G-O, Kidney Disease
4 Improving Global Outcomes guidelines, or the 2024
5 ADA guidelines, American Diabetes Association
6 guidelines, recommend -- recommend, in the case of
7 GLP-1 receptor agonist, recommend -- the most
8 specificity on the recommendation is one of the
9 agents that has been shown to have demonstrated
10 efficacy in large, randomized CVOT trials, that's
11 cardiovascular outcome trials, and these include
12 semaglutide, liraglutide and dulaglutide, as
13 potential agents to treat -- or to administer to
14 patients with chronic kidney disease in the
15 setting of type 2 diabetes.

16 Q Those guidelines you referred to, the
17 KDIGO guidelines, those issued prior to this New
18 England Journal of Medicine article, correct?

19 A Correct.

20 Q And is it fair that guidelines
21 generally don't recommend one GLP-1 over another?

22 MR. ANSTAETT: Objection. Form.

1 A In general, I have -- what I've seen is
2 that the -- again, there's not a specific -- a
3 specific one called out for, right?

4 Q And is that because guidelines
5 typically do not call out a specific therapy?

6 MR. ANSTAETT: Objection. Form.

7 A The motivation behind it is probably
8 complex, but, in general, that statement is
9 correct. They don't necessarily -- or generally
10 call out a specific therapy.

11 Q The guidelines rely on the physicians
12 to make a choice on which one will actually be
13 best for a particular patient?

14 MR. ANSTAETT: Objection to form.
15 Foundation.

16 A Yes, physicians have the final say in
17 what they end up prescribing. Again, it's an
18 interplay with the patient's experience, whether
19 they've been on an agent or not, and whether they,
20 again, the way the insurance is structured in this
21 country, and where you practice, so it can -- it
22 obviously just varies on which one you can get

1 covered. And so, the general rule of thumb,
2 again, that I -- we practice in our clinics, at
3 Mount Sinai, is one of the agents in the class
4 would serve to be in the best interest of the
5 patients.

6 Q So to be clear, you don't ever
7 recommend one GLP-1 over the other?

8 A That is correct. We do not recommend
9 one GLP-1 over another.

10 Q Are you still considering the
11 significance of the New England Journal of
12 Medicine article?

13 MR. ANSTAETT: Objection. Form.

14 A Can you be more specific about the
15 significance?

16 Q Is it going to -- are you still
17 considering whether and how it will impact your
18 recommendations going forward?

19 A I can tell you this, Josh: Given that
20 both the design trial -- the design paper for the
21 FLOW trial, and Peter Rossing is the first author,
22 and I think it's one of our exhibits, and the

1 wording of the discussion in the FLOW trial,
2 all -- the way I interpret it, and I think most
3 experts would interpret it, is that this was
4 generally viewed as a largely class-effective
5 GLP-1 receptor agonist.

6 There's a -- in the design paper, it
7 was clearly stated that multiple agents within the
8 GLP-1 receptor agonist class appeared to have
9 kidney-protective properties, and that was used to
10 support the design of the FLOW trial.

11 And then, the discussion, itself,
12 states that semaglutide and other GLP-1 receptor
13 agonists now have the potential to be used in
14 diabetic kidney disease, and the references that
15 were provided in the discussion, regarding the
16 potential mechanistic, again, all speculative, on
17 the potential mechanisms of benefit for
18 semaglutide, in this case, in the FLOW trial,
19 refer to articles that discuss the GLP-1 receptor
20 agonist, again, largely, in a class, and details,
21 within those articles, also cited papers that
22 showed protective properties of the GLP-1 peptide,

1 various GLP-1 receptor agonists, et cetera, and
2 were not specific to semaglutide.

3 Those are references 20 to 23 in the
4 FLOW trial, to be specific.

5 Q So the -- is there a shorthand that I
6 can call this article, that we can agree to, for
7 the rest of this deposition? Is there something
8 you're comfortable calling it?

9 A The FLOW manuscript.

10 Q Okay. So in your opinion, because the
11 FLOW manuscript cites to articles about other
12 GLP-1s, persons of skill would understand the FLOW
13 manuscript to apply to GLP-1s as a class?

14 A Again, it's not just a citation from
15 FLOW. It's the design paper that, also, the
16 wording there was very holistic in terms of
17 potential class effect, from the GLP-1 receptor
18 agonist, as a motivation for the design of the
19 FLOW. Coupled with those references, coupled with
20 guidelines, which, again, generally don't support,
21 coupled with real life, again, where it is not the
22 norm to single out one agent just because it was

1 the one that happened to be studied in a large
2 definitive trial, such as FLOW, where
3 meta-analyses, whether on the clinical kidney end
4 points that were softer or large cardiovascular
5 outcome trials, which there are many now of the
6 GLP-1 receptor agonist, show relative homogeneity
7 of effect for cardiovascular and soft clinical
8 outcomes.

9 So, to me, it would be strange, now,
10 to, then, pivot and just say, oh, only semaglutide
11 because it was the one that was studied in the
12 FLOW trial.

13 Q But you agree no other GLP-1 was
14 studied in the FLOW trial, correct?

15 A Correct. But absence of evidence is
16 not evidence of absence. And, again, when you
17 talk a totality of the picture, the animal data,
18 for two decades leading into the FLOW trial, was
19 not specific to only semaglutide on potential
20 kidney-protective effects. We know that multiple
21 GLP-1 receptor agonists control not only
22 glycemic -- not only glycemia diabetes but, also,

1 cause -- help with weight loss and blood pressure
2 control, which are very important clinical factors
3 in managing someone with diabetes, along with the,
4 again, the author's own words that really infer
5 that this is likely a class effect. I think we
6 have, again, you have -- you're triangulating
7 multiple lines of evidence, data, hypotheses, and
8 conclusions that suggest various GLP-1 receptor
9 agonists would be effective for diabetic kidney
10 disease, had they been -- and it's just that FLOW
11 was the one that studied one agent in this large
12 trial.

13 Q You refer to the animal data for nearly
14 two decades.

15 Do you recall that?

16 A Yes.

17 Q Did any of that animal data demonstrate
18 reduction in mortality in humans?

19 A To support a protective effect on the
20 kidneys of any agent, you wouldn't necessarily
21 conduct an animal study to look at mortality.
22 There are other much more viable ascertainment in

1 animal models to try to deduce whether there are
2 kidney-protective properties.

3 Q I'm not sure you quite answered my
4 question, so I'll just try it one more time.

5 Did any of the animal data that you
6 referenced demonstrate a reduction in mortality --

7 MR. ANSTAETT: Objection to form.

8 Q -- yes or no?

9 A I'm not -- to my knowledge, I don't
10 recall if any of them actually studied mortality,
11 but it's not a typical endpoint in animal studies.
12 Those are clinical trials that would look at
13 mortality. And it wouldn't be the endpoint for
14 any -- a kidney animal study.

15 MR. REICH: I think now is a good time
16 for a break. I don't know about you, Dr. Coca.

17 Do you want to take ten minutes?

18 THE WITNESS: Sure. Thanks, Josh.

19 (Recess taken from 10:52 a.m. to
20 11:04 a.m.)

21 BY MR. REICH:

22 Q So, Dr. Coca, earlier, you had

1 mentioned some animal data, correct?

2 A Yes.

3 Q You had also mentioned some human
4 trials, correct?

5 A Yes.

6 Q If you had conflicting results between
7 an animal study and in-human trial, which study
8 would you credit?

9 MR. ANSTAETT: Objection. Form.

10 A Josh, that's a complicated question
11 because it depends on the study design of either.
12 There's well-done and poorly designed animal
13 studies, and there's well-done and poorly designed
14 human studies.

15 I'm certain some -- you know, some
16 things have failed to translate maybe because of,
17 you know, design and bias issues. So it runs a
18 gamut. It's tough so say without looking at the
19 individual studies, Josh.

20 Q The articles you studied -- you cite in
21 your declaration, were those well-designed, in
22 your opinion?

1 MR. ANSTAETT: Objection. Form.

2 A Generally, they were -- there was no --
3 there was no obvious poorly designed, off the bat,
4 but, certainly, some were better quality than
5 others. But, again, if we want to talk specifics,
6 we can do that. But it's hard to make blanket
7 statements.

8 Q Did you identify which studies were
9 better designed, in your declaration?

10 MR. ANSTAETT: Objection. Form.

11 A No, I did not perform a comprehensive
12 quality assessment on each study.

13 Q So, in general, in your declaration,
14 for the studies you discussed, if there's a
15 conflicting answer between an animal study and an
16 in-human study, which one would you credit?

17 MR. ANSTAETT: Objection. Form.

18 A Again, I -- I would need to see the
19 specific animal studies and the specific human
20 study to see the potential reasons for the
21 discrepancy.

22 Q So sitting here today, you can't tell

1 me, one way or the other, whether you would credit
2 the results from an animal study or an in-human
3 study, if there were conflicting results?

4 MR. ANSTAETT: Objection. Form.

5 A Josh, it depends. It depends on the
6 study. Animal or human doesn't make one more
7 right than the other. It depends.

8 Q Is an animal study sufficient to
9 indicate that it will have -- strike that.

10 Is an in-animal study sufficient to
11 indicate that the results will likely translate to
12 in-human trials?

13 MR. ANSTAETT: Objection. Form.

14 A No. They're not sufficient in and of
15 themselves. You want to look at the totality of
16 evidence across the animal studies, and then,
17 corroboration in clinical studies. Again, you're
18 trying to develop a complete picture in this --
19 especially for kidney disease, again, which is a
20 complex syndrome, it's not one molecular switch
21 that's turned on. It's complex. You want to use
22 multiple lines of data and evidence to generate

1 hypotheses and to support conclusions.

2 MR. REICH: Can we pull up paragraph 77
3 of Dr. Coca's declaration, Exhibit 1306. It's on
4 page 39.

5 PLANET DEPOS TECHNICIAN: Stand by.

6 Q Dr. Coca, you write "it is
7 well-established in the art by 2010 that GLP-1
8 agonists demonstrated, at a minimum,
9 kidney-protective effects, and were, in fact,
10 likely to directly treat CKD and DKD."

11 Do you see that?

12 A Yes.

13 Q And is it a fair understanding, in your
14 declaration, that the next several paragraphs,
15 going up through 85, are the support that you have
16 for that assertion?

17 MR. ANSTAETT: Objection to form.

18 A Yeah, several -- through 85, I'm citing
19 several demonstrations of the potential
20 kidney-protective effect of GLP-1 and GLP-1
21 receptor agonists, through 85, yes.

22 (Coca Exhibit 3 marked for

1 identification and attached to the transcript.)

2 Q So the first article you rely on is
3 Exhibit 1148, by you.

4 Do you see that in paragraph 77?

5 A Yes, I see that.

6 Q And this was administering recombinant
7 GLP-1; is that correct?

8 A I believe so.

9 Q And if at any point you want to see any
10 of these articles, let me know and I'll pull them
11 up. But, you know, happy to do that. But,
12 otherwise, just for efficiency.

13 A Sure.

14 Q And is recombinant GLP-1 a version of
15 native GLP-1?

16 A I'm not a chemist, but it should mimic
17 the biologic actions of the native.

18 Q It's not a GLP-1 analogue, correct?

19 A Well, it's the peptide. I'm not sure
20 what you're trying to get at. It's trying to
21 mimic the human protein.

22 Q It hasn't been modified, for example?

1 MR. ANSTAETT: Objection to form.

2 A Josh, I'm not sure on the exact
3 chemistry structure that was used in that study.

4 Q Okay. And in Exhibit 1148, the
5 recombinant GLP-1 was administered to Dahl
6 sensitive rats; isn't that correct?

7 A Correct.

8 Q Is there anything that you saw in --
9 strike that.

10 Do you know of any conclusions the
11 authors draw as to how this will impact humans?

12 MR. ANSTAETT: Objection to form.

13 A Josh, I don't remember the details of
14 Exhibit 1148's conclusion. If we want to pull it
15 up, we can see. I don't know if they speculated.
16 Again, this was early on in the investigations and
17 the time course of GLP-1 and kidneys. So --

18 MR. REICH: Sean, could you, please,
19 share Exhibit 1148 with Dr. Coca and everyone
20 else.

21 PLANET DEPOS TECHNICIAN: Stand by.

22 Q While he's doing that, you at least

1 agree, Dr. Coca, that in paragraph 77, you didn't
2 note any conclusions the authors drew with how
3 GLP-1 would impact humans; is that correct?

4 A That statement is correct. I did not
5 note it.

6 MR. ANSTAETT: Josh, I'll let you know
7 when it shows up in the folder.

8 PLANET DEPOS TECHNICIAN: Counsel, I
9 just posted it.

10 MR. ANSTAETT: I see it in there.
11 Okay. I have it. I have it as well.

12 And, Dr. Coca, I know it's pulled up on
13 your screen. I don't know if you have the ability
14 to scroll through it.

15 Does he have the ability to do that or
16 not?

17 PLANET DEPOS TECHNICIAN: Absolutely,
18 Counsel, I can get him remote access.

19 MR. ANSTAETT: Okay.

20 PLANET DEPOS TECHNICIAN: Would you
21 have me give him access, Counsel?

22 MR. REICH: Yeah. Please feel free,

1 give Dr. Coca access.

2 A Well, actually, in their conclusion,
3 they are alluding to -- they do make the leap to
4 potentially suggest there would be a useful-type
5 strategy in humans with salt-sensitive forms of
6 hypertension and other conditions of -- associated
7 with sodium retention, such as heart failure. So,
8 even though they don't say the word "human"
9 specifically, I mean, that's what they're alluding
10 to.

11 Q Beginning -- I'm sorry.

12 A No, go ahead.

13 Q So, they did not test this in humans,
14 agree?

15 A Agree, no. Certainly not.

16 Q The first sentence of the summary says
17 that it improves endothelial function in Dahl S
18 rats, correct?

19 A Correct.

20 Q And this is recombinant GLP-1, correct?

21 A Correct.

22 Q And in the middle of the conclusion it

1 says "Due to the short half-life and the lack of
2 oral bioavailability, therapeutic potential of
3 rGLP-1, itself, for the treatment of hypertension,
4 is probably very limited."

5 Do you agree with that?

6 A That's what it states.

7 Q And it points to the potential for an
8 orally active and stable GLP-1 analogue that might
9 be useful for the treatment of salt-sensitive
10 forms of hypertension.

11 Do you see that?

12 A I see that.

13 MR. ANSTAETT: Josh, you said something
14 about the exhibit, but I didn't catch it.

15 MR. REICH: Yeah, sorry.

16 Q Dr. Coca, is there any data on GLP-1 in
17 here, in this article?

18 A GLP-1 receptor antagonist.

19 Q Or native GLP-1 or other GLP-1 analogs?

20 A Again, this is one of the multiple
21 pieces of evidence. This was early on, this was
22 2003, just showing that this pathway is

1 potentially relevant in treating, in this case,
2 hypertension. There were -- above, there were the
3 kidney assessments that were done with the
4 histology, showing less kidney damage.

5 It's a common feature of animal studies
6 that look at blood pressure control to see
7 whether -- the effects on the kidney architecture
8 and kidney function.

9 So, again, this was just one of the
10 multitudes of early demonstration that this GLP-1
11 pathway is potentially druggable and may have
12 benefits in chronic cardiovascular kidney
13 conditions.

14 Q But to confirm, the only data is on
15 recombinant GLP-1, correct?

16 A From this paper. Again, I wouldn't
17 rely on one paper, alone, to make any conclusion.

18 Q And it's -- I think you said its focus
19 was on hypertension, correct?

20 MR. ANSTAETT: Object to form.

21 A Well, the Dahl sensitive rats are a
22 hypertensive model that investigators use to --

1 they use it as a cardiorenal model, since these
2 rats, that are salt-sensitive, when they're given
3 a high-salt diet, typically get hypertension and
4 organ damage. So it's a nice model to study
5 potential -- potential interventions in this
6 condition.

7 Q If we could go back to Exhibit 1306. I
8 think we'll be shuffling back and forth a bit, but
9 paragraph 78 on page 39.

10 A Yes.

11 Q Are you there, Doctor?

12 A Yes. Paragraph 78, page 39.

13 MR. REICH: If you'd scroll down just a
14 little, Sean.

15 (Coca Exhibit 4 marked for
16 identification and attached to the transcript.)

17 Q So are you familiar with Exhibit 1147?
18 It's an article by Vollenweider. I might be
19 butchering that.

20 A Yeah, I had initially reviewed it for
21 the declaration. Again, I may not remember every
22 detail.

1 MR. REICH: Can we share Exhibit 1147,
2 please, Sean.

3 PLANET DEPOS TECHNICIAN: Stand by.
4 Exhibit 1147 is up.

5 Q And you can take a second to look
6 through this, Dr. Coca.

7 MR. ANSTAETT: Sean, I know you're
8 probably working on it, but if you could put it in
9 the chat, that would be great.

10 When I say, "in the chat," I mean in
11 the folder.

12 PLANET DEPOS TECHNICIAN: Sure,
13 Counsel. Stand by.

14 A Josh, is there a specific question on
15 this manuscript?

16 Q Yep. So Exhibit 1147 is discussing
17 native GLP-1 in Dahl S rats; is that correct?

18 A Yes, actually, this is -- it's a
19 perspective piece, largely written in conjunction
20 with the Yu paper, so it's kind of taking the
21 findings by Yu, in Exhibit 1148, and putting them
22 into bigger context.

1 Q And Exhibit 1147 notes that the role
2 remains obscure for GLP-1 receptors in the kidney?

3 MR. ANSTAETT: Can you direct us where,
4 in the article, you're reading from, Josh?

5 MR. REICH: Midway down the left, first
6 page.

7 Q Dr. Coca, you just read it, so I assume
8 you saw it.

9 A I see GLP-1 receptors are abundant in
10 the kidney, but their role remains obscure.

11 Q And on the top right of page 1, do you
12 see where it says "Whether these effects of GLP-1
13 are mediated through renal GLP-1 receptors remains
14 unanswered"?

15 A I see that.

16 Q Is that referring to the hypertensive
17 effects from Yu?

18 A Yes.

19 Q And then, the next paragraph, right
20 after that, is discussing that in concluding that
21 further experiments are required to address the
22 impacts on hypertensive action; is that correct?

1 A Correct.

2 Q So this article, that goes with Yu at
3 the time, concludes that, at best, Yu just says,
4 go to further experiments to confirm or look into
5 this issue?

6 MR. ANSTAETT: Objection to form.

7 A Again, this is part of the litany of
8 early literature two decades ago. The first was
9 elucidating the role of GLP-1 in, again, diabetes,
10 hypertensive disease, et cetera. And so, I think
11 they're -- the authors of both papers, we've just
12 recently discussed, are trying to provide their
13 findings, you know, in modesty, without
14 overstepping conclusions, because that's the way
15 science works. You don't do one experiment and
16 then make overly presumptuous conclusions.

17 It's a very frequent mantra that more
18 research is needed and I -- again, at this stage,
19 since this was early in the paradigm, I think it's
20 the appropriated thing to say.

21 Q Do you think Yu demonstrated that GLP-1
22 had a diuretic and strong natriuretic action

1 resulting in a negative cumulative sodium balance?

2 A We can -- hold on. I took that -- for
3 paragraph 78, that line is directly -- let me see
4 where it's -- where does he state it? Oh, here.
5 That was reference 4, which was Yu, which is our
6 Exhibit 1148.

7 Can we go back to 1148 and find the
8 actual primary data on the sodium balance, if
9 that's what you're interested in?

10 Q No, I'm interested -- you wrote, in
11 paragraph 78, "Other studies also demonstrated
12 that GLP-1 had a diuretic and strong natriuretic
13 action resulting in negative cumulative sodium
14 balance." And you cited Exhibit 1147 at 1.

15 Do you see that?

16 A Yes.

17 Q I believe what you quoted is exactly
18 where you went to, on page 1147. So if you can
19 scroll back up so we're all looking at the same
20 thing.

21 And it appears what you cut off from
22 the quote was "additional experiments indicated

1 that GLP-1 had a" strong -- "had a diuretic and
2 strong natriuretic action."

3 Do you see that?

4 A Yes.

5 Q So you took a quote that went from --
6 that stated indicated, and you have now said that
7 it was demonstrated.

8 Do you see that?

9 MR. ANSTAETT: Objection to form.

10 A I wouldn't make such a big deal about
11 the semantics of indicate versus demonstrate. But
12 let's go back to 1148 to see because the words
13 "strong natriuretic action," of course, that
14 adjective can be open to interpretation, so we can
15 quantify the natriuretic effect, if that would
16 help.

17 Q No. In paragraph 78, when you said
18 "other studies," you were only referring to Yu; is
19 that correct?

20 By Yu, I mean 11 -- Exhibit 1148.

21 A Yeah, it is circling back to the Yu
22 study, which was paragraph 77, so --

1 Q And again --

2 A -- no one's --

3 Q Sorry. I didn't mean to cut you off.

4 A No, it's just that -- so maybe it
5 should have said "other experiments." Because in
6 the Yu study, you know, these animal studies are
7 typically not one -- are not necessarily just one
8 group of rats that they -- there must have been
9 multiple -- there was clearly multiple time points
10 and experiments within the Yu paper so that they,
11 again, you put together a story of, you know,
12 there's more natriuresis, there's less -- better
13 kidney function, there's less kidney damage on
14 histology, things like that.

15 So it's -- so perhaps in paragraph 78,
16 other studies would be other experiments. But it
17 was referring to the primary data reflected in the
18 Yu study, Exhibit 1148.

19 Q And if we turn to Exhibit 1147 at
20 page 2, and it says, at the top of the first
21 paragraph, "The results contrast with previously
22 published data showing that GLP-1 or GLP-1

1 receptor agonist administration acutely increased
2 blood pressure and heart rate in rats."

3 Do you see that?

4 A I see that.

5 Q Okay. Did you address this discrepancy
6 at all in your declaration?

7 A No, I did not.

8 Q Is this picture settled, as you made it
9 out to be, in paragraph 78?

10 (Coca Exhibit 5 marked for
11 identification and attached to the transcript.)

12 MR. ANSTAETT: Objection. To form.

13 A Well, Josh, there were -- at that --
14 and in paragraph 79, we have additional studies,
15 Exhibit 1149, Gutzwiller, which showed a
16 natriuretic effect supporting the Yu findings, and
17 further studies by Gutzwiller, outlined in
18 paragraph 81, and I would say -- and then in -- up
19 to -- paragraph 83 of the declaration, 2010, Liu
20 showed GLP-1 can promote salt and water secretion
21 so that's, again, natriuresis. And then, I would
22 also like to point out that the clinical data

1 support the Yu findings with the frequently
2 observed reduction of blood pressure that was seen
3 in Phase II and Phase III studies of various GLP-1
4 receptor agonist.

5 Q Okay. But in paragraph 79, which was
6 what I asked about -- or, I'm sorry --

7 A 78.

8 Q -- paragraph 78, you didn't mention
9 that Exhibit 1147, by Vollenweider, discussed that
10 these results actually contrasted with previously
11 published data; is that correct?

12 MR. ANSTAETT: Objection to form.

13 A Correct.

14 Q Okay. And if we go midway down in this
15 paragraph and page 2 of Exhibit 1147, it says
16 "Acute administration of GLP-1 increases blood
17 pressure in healthy subjects, whereas blood
18 pressure remained unchanged in diabetic patients
19 treated over 6 weeks."

20 Do you see that?

21 MR. REICH: Please scroll down a bit
22 more.

1 Q I think my question was just, do you
2 see that sentence?

3 A I see that sentence.

4 Q And you read the next sentence, which
5 states "Clearly, long-term studies are needed to
6 settle this issue and ideally such studies should
7 include subjects with salt-sensitive forms of high
8 blood pressure."

9 Do you see that?

10 A I see that.

11 Q Do you have any reason to disagree with
12 their conclusion that "clearly, long-term studies
13 are needed to settle this issue"?

14 MR. ANSTAETT: Objection to form.

15 A I agree that this was very early on.
16 They're only using the peptide. I don't know how
17 much of this acute administration, that's not the
18 way -- obviously, now, this has been --
19 fast-forward through most recent years, in the
20 current era, we don't -- we don't infuse GLP-1
21 itself. Obviously, there's been a lot of
22 increased understanding and tinkering with these

1 agents to make them more suitable for clinical
2 administration. And so, clearly, the conflicting
3 results, the ones that show higher blood pressure,
4 are not reflective of the way the agents actually
5 act in humans.

6 So --

7 Q But that -- I'm sorry.

8 A Okay.

9 Q Did that --

10 A You can finish.

11 Q Are you finished?

12 A I would just consider this early --
13 this early -- this early, you know, feeling out
14 the situation, again, on how to best understand
15 this pathway, how to target this pathway. Again,
16 these were peptide infusions, and it doesn't
17 surprise me that there can be conflicting data at
18 this early stage because of various
19 pharmacokinetic reasons, and they allude to the
20 half-life issues, et cetera, that are here with
21 this peptide, and they allude, at the bottom here,
22 that the analogs, with different half-lives, will

1 help overcome some of the situations, and what
2 they're referring to is the design issues in these
3 animal studies and the way this peptide is
4 degraded, so.

5 Q Dr. Coca, you used multiple studies
6 about Dahl S rats to support your opinions about
7 what would be expected in humans; is that fair?

8 A No, not completely. I used some Dahl S
9 rat studies as one of the multitude of the
10 components of evidence that support GLP-1 as a
11 potential kidney-protective pathway.

12 Q We'll walk through some of the other
13 articles, right? But at least as one component of
14 your support for your conclusions, you relied on
15 Dahl S rat studies and you opined that those would
16 be relevant or indicative as to how these GLP-1
17 receptor agonists might operate in humans; is that
18 fair?

19 MR. ANSTAETT: Objection to form.

20 A It's just one line of evidence. If it
21 was the only data out there, then I would be
22 concerned. But it's just one in a long litany of

1 further evidence that emerged following the early
2 2000s here, so...

3 Q And in Exhibit 1147, their actual
4 conclusion was that with such new tools, referring
5 to the longer-acting analogs, it would be possible
6 to test whether the antihypertensive actions of
7 GLP-1, seen in Dahl salt-sensitive rats, are also
8 encountered in human disease states.

9 Do you see that?

10 A I see that.

11 MR. ANSTAETT: And objection to form.

12 Q So these authors didn't conclude that
13 these will be expected in human disease states,
14 fair?

15 MR. ANSTAETT: Objection to form.

16 A Fair. And I give them credit for not
17 overstating what these results mean.

18 Q Well, we'll talk about overstating the
19 results.

20 If we could turn to paragraph 79 of
21 Exhibit 1306.

22 I guess, for the record, do you think

1 you overstated any of the results in paragraph 77
2 or 78 as it relates to 1147 and Exhibit 1148 as
3 they relate to Dahl S rats?

4 MR. ANSTAETT: Objection to form.

5 A No, because, A, I took direct quotes
6 from the studies and the authors themselves and,
7 B, the -- like, for example, in 78, where it
8 says -- I used the language "may be attributable
9 to a direct effect on the kidneys." Again,
10 science builds upon itself and studies the
11 reproducibility and the amounts of data build
12 on -- and support hypotheses and build on the
13 evidence.

14 Q Let's go to paragraph 79 of
15 Exhibit 1306. It's on page 40, Sean, please and
16 thank you.

17 I don't think I covered this earlier,
18 Dr. Coca, if at any point you need a break, just
19 let me know and I'll do my best to accommodate.

20 A Okay. Thanks, Josh.

21 Q So, do you see in paragraph 79 you
22 wrote, "It was documented that GLP-1 infusion dose

1 independently increased sodium secretion and had a
2 natriuretic effect in obese, insulin-resistant
3 patients who suffered from type 2 diabetes."

4 Do you see that?

5 A I see that.

6 Q And you cite Exhibit 1149 as support?

7 A Yes.

8 Q Do you think it's a fair
9 characterization of Exhibit 1149 that this was
10 shown, this natriuretic effect was shown in the
11 patients who suffered from type 2 diabetes? And I
12 note that that's a quotation.

13 MR. ANSTAETT: Objection to form.

14 And just for the record, Josh, you note
15 that it's a quotation from the article, not from
16 his report?

17 Q Correct. For the record, Dr. Coca,
18 this is what you have put as a quote from
19 Exhibit 1149.

20 A Correct.

21 Q Do you agree, do you think that is a
22 fair characterization of Exhibit 1149?

1 A I do. But I'd be happy to review the
2 data jointly.

3 Q Yep. Let's do that. Let's share --
4 Sean, please share Exhibit 1149.

5 PLANET DEPOS TECHNICIAN: Stand by.

6 MR. REICH: And, Dave, if you'd let me
7 know when you get it, then I'll proceed with
8 questioning. I'll wait for you. I know I jumped
9 the gun a couple times.

10 MR. ANSTAETT: Yeah, sure. I'll let
11 you know when it's up.

12 MR. REICH: Appreciate that.

13 PLANET DEPOS TECHNICIAN: Exhibit 1149
14 is up.

15 MR. ANSTAETT: Okay. I have it.

16 BY MR. REICH:

17 Q Dr. Coca, you see the title is
18 "Glucagon-Like Peptide 1 induces Natriuresis in
19 Healthy Subjects and in Insulin-Resistant Obese
20 Men."

21 Do you see that?

22 A Yes, glucagon-like peptide, yes.

1 Q Thank you. I'll try to pronounce that
2 better.

3 MR. ANSTAETT: Do you have the access
4 to scroll?

5 MR. REICH: No. We can go -- that
6 citation, from paragraph 79 to Exhibit 1149, was
7 to page 6.

8 MR. ANSTAETT: 6.

9 Q Could you show me where on page 6, or
10 anywhere else, this quote is found?

11 A I cannot find the exact quote. The
12 first sentence under discussion is very similar,
13 but -- instead of --

14 Q I don't want to cut you off. I can ask
15 a question, but if you were about to continue
16 speaking, please, finish your thought.

17 MR. ANSTAETT: And if you need time
18 with one of the articles, take the time you need.

19 MR. REICH: Yep. Take all the time you
20 need.

21 A Well -- well, Josh, what I see is that
22 I can't find the exact quote, but I would say the

1 spirit of the line and then, perhaps, I shouldn't
2 have used exact quotations, is supported by the
3 data. And I can point to here the factual
4 excretion of sodium in Table 2, with the lower
5 dose versus the higher dose of GLP-1, the
6 secretion increased from 1.7 to 2.7 percent.

7 Q Can we pause there? Just for the
8 record --

9 A Yes.

10 Q -- you were referring to Table 2,
11 correct?

12 A Table 2, reaction excretion sodium, as
13 well as sodium secretion in millimoles.

14 Q Yes or no, the data you're --

15 MR. ANSTAETT: Wait, Josh. You're
16 interrupting him. You're cutting him off. You
17 can ask your question when he's done answering.

18 MR. REICH: It's been a five-minute
19 answer, Dave.

20 MR. ANSTAETT: It has not been a
21 five-minute answer. And you asked him to read a
22 seven-page document.

1 MR. REICH: That's not what I asked him
2 to do.

3 MR. ANSTAETT: It is what you asked him
4 to do.

5 MR. REICH: It's time-stamped, Dave.
6 The record will reflect how long this has been.

7 MR. ANSTAETT: It will. And it will
8 reflect that you're asking him to read a
9 seven-page document and find a quote in it, Josh,
10 and he's answering your question, and cutting him
11 off doesn't help your --

12 MR. REICH: I'll note that what you're
13 saying is it's supported and then you went on a
14 whole bunch of other stuff, so I'm trying to make
15 the record clear about what he's answering.

16 MR. ANSTAETT: I think what you're
17 doing is the opposite of making a record clear.
18 But in any case, he's entitled to answer, and then
19 you can ask your next question.

20 BY MR. REICH:

21 Q Yep. Please proceed, Dr. Coca.

22 A Well, what I'm also realizing, in

1 clarification, is that Table 2 is reflective of
2 healthy subjects and not the obese,
3 insulin-resistant subjects. So we need to, then,
4 look at Figure 4, which is the data in the obese
5 subjects, which shows the -- panel A of Figure 4
6 shows the increase in sodium excretion of GLP-1
7 versus placebo, both as a group, where it appears
8 to from about 60 millimole per 180 minutes to
9 about close to 100, as a group. And then, on the
10 left part of panel A are the individual line plots
11 of the patients showing those changes between
12 placebo and GLP-1 and many of the patients have an
13 increase in sodium excretion.

14 Q Are you done answering?

15 A I'm done answering.

16 Q So I think what I had asked was, do you
17 see that quote appear? And if you could just give
18 me a yes or no. I'll ask more questions, but --

19 A Okay.

20 Q You had -- in paragraph 79 and you
21 cited to Exhibit 1149, page 6.

22 Do you see that?

1 A I see that.

2 Q And does that quote appear after you've
3 reviewed Exhibit 1149, does that quote appear
4 anywhere in Exhibit 1149, yes or no?

5 A No, I do not see it.

6 Q And if we go to page 6, and I'll note,
7 for the record, that you're able to scroll. If we
8 go to page 6, at the discussion, I think what it
9 appears you actually were trying to quote is the
10 sentence that states "Here, we have documented
11 that GLP-1 infusion dose-dependently increases
12 urinary sodium excretion in healthy male
13 volunteers."

14 Do you see that sentence?

15 A Yes, I do.

16 Q There's a big difference between what
17 you quoted, about it demonstrating this in
18 patients who suffered from type 2 diabetes, and
19 what the actual quote is, about it being
20 demonstrated in healthy male volunteers.

21 Do you agree?

22 MR. ANSTAETT: Objection to form.

1 A Agree it was -- the dose dependency was
2 witnessed in the healthy male volunteers and
3 natriuretic effect was confirmed in the obese,
4 insulin-resistant patients, 25 percent of whom
5 had -- were suffering from type 2 diabetes.

6 Q So to confirm, not all of the obese
7 patients suffer from type 2 diabetes, correct?

8 A Correct.

9 Q And you pointed to a figure, if you
10 could just scroll up, we can look at that real
11 quick.

12 For the record, this is Figure 4A you
13 were referring to, correct?

14 A Correct.

15 Q Does this identify which of those
16 patients were the four that had type 2 diabetes?

17 MR. ANSTAETT: Objection to form.

18 A No, it doesn't.

19 Q And some of those lines seem to
20 decrease while other decreased [sic].

21 Do you see that?

22 MR. ANSTAETT: Objection to form.

1 A I only see one line that substantially
2 decreases.

3 Q And looks like there are three other
4 lines that may be, at best, are flat?

5 MR. ANSTAETT: Objection to form.

6 A Perhaps. I can't tell for sure.
7 That's a --

8 Q And the initial evidence you went to,
9 to support the spirit of your quote, was the data
10 from Table 2, which was the healthy male patients,
11 correct?

12 MR. ANSTAETT: Objection to form.

13 A Correct.

14 Q And the --

15 MR. REICH: We can take that down and
16 go back to Exhibit 1306.

17 Q Dr. Coca, let me know when you have
18 paragraph 80 in front of you.

19 A I have it.

20 Q I don't know if you can scroll, but if
21 you can scroll down to paragraph 80, that would be
22 great.

1 And in paragraph 80 you write that the
2 prior art study being discussed described GLP-1 as
3 being able to "reverse this vicious cycle" and
4 represented a new treatment regimen for patients
5 with type 2 diabetes.

6 Do you see that?

7 A I see that.

8 Q And this is also referring to
9 Exhibit 1149?

10 A I believe so.

11 MR. REICH: Sorry to do this, Sean. If
12 you could pull back up Exhibit 1149.

13 If we could go to page 7 of the PDF.

14 Q So while you describe these prior art
15 studies as describing GLP-1 as being able to
16 reverse this vicious cycle, we go ahead down to
17 the last paragraph on page 7.

18 Do you see the actual citation is -- or
19 actual quote is "we speculate that GLP-1 could
20 reverse this vicious cycle."

21 Do you see that?

22 A I see that.

1 Q Do you think you overstated the
2 conclusion that Exhibit 1149 drew at all?

3 MR. ANSTAETT: Objection to form.

4 A Perhaps including the word "could"
5 would be prudent.

6 Q And maybe that they were speculating?
7 Would that have also been prudent to include?

8 MR. ANSTAETT: Objection. Form.

9 A I guess the word "could" adds a notion
10 of speculation.

11 MR. REICH: And -- I think now would be
12 a good breaking point, if you guys want to do
13 lunch, or we can keep going. Up to you.

14 MR. ANSTAETT: It's really up to you.

15 THE WITNESS: Can I go on mute a
16 second?

17 MR. ANSTAETT: How much more do you
18 have, Josh?

19 MR. REICH: Sorry, Dave, I missed that.

20 MR. ANSTAETT: How much more do you
21 think you have?

22 MR. REICH: Hard to say. It depends on

1 pace, but we won't be here until 7:00 p.m.,

2 Dr. Coca. I promise you that.

3 MR. ANSTAETT: Your deposition was
4 limited of Dr. Coca, in terms of time, if you
5 recall, and we will abide by the time you
6 suggested.

7 MR. REICH: And what was the time?

8 MR. ANSTAETT: Four hours.

9 MR. REICH: Four hours? Okay.

10 MR. ANSTAETT: How much time do we have
11 on the record, Judy, if you could possibly tell
12 us?

13 MR. REICH: I guess we can go off the
14 record while we're discussing this so it's not all
15 over the transcript.

16 MR. ANSTAETT: Yes, that's fine.

17 (Off the record.)

18 BY MR. REICH:

19 Q Dr. Coca, what did you discuss with
20 counsel over break?

21 MR. ANSTAETT: One second. You're not
22 entitled to ask him what he discussed with his

1 counsel.

2 MR. REICH: Yes, I am.

3 MR. ANSTAETT: According to what?

4 MR. REICH: The PTAB rules.

5 MR. ANSTAETT: No. If it's in the PTAB
6 rule that says that you're entitled to ask for
7 conversations between lawyers and their experts,
8 I'll let you ask it. And it says what you says it
9 says, I'll let you ask it at the end.

10 MR. REICH: So you're instructing
11 Dr. Coca to not answer what you and him discussed
12 during break, in the middle of the deposition?

13 MR. ANSTAETT: Yeah. But I'm giving
14 you the opportunity, if you have authority that
15 you think says that's a proper question, we'll
16 consider it and let you ask it before the
17 deposition's over, if I agree.

18 MR. REICH: Okay.

19 BY MR. REICH:

20 Q Dr. Coca, yes or no, did you discuss
21 the substance of your testimony with counsel over
22 break?

1 A No.

2 MR. ANSTAETT: You can answer that yes
3 or no.

4 A No.

5 Q Okay. Turning to paragraph 81 of your
6 report, please, Dr. Coca.

7 MR. REICH: Which is Exhibit 1306,
8 Sean.

9 (Coca Exhibit 6 marked for
10 identification and attached to the transcript.)

11 Q Do you see you cite Exhibit 1163 for
12 support of your assertion that Gutzwiller
13 characterized GLP-1's renal effects and looked
14 specifically at the mechanism by which GLP-1 was
15 inducing a reduction in internal -- intestinal
16 sodium absorption?

17 Do you see that?

18 A Yes.

19 Q Do you mention, in paragraph 81, in
20 discussing Exhibit 1163, that the study was in
21 healthy male subjects?

22 A No.

1 Q Do you think that's pertinent
2 information?

3 MR. ANSTAETT: Objection to form.

4 A It may or may not be. I think, at this
5 point, people are just trying to characterize what
6 could GLP-1 effects on the kidneys or sodium
7 handling are operative. And so, whether or not
8 it's tested in type 2 diabetes or not, it still
9 gives you some indication of physiology.

10 Again, no single piece of evidence is
11 sufficient.

12 Q You agree it was in healthy male
13 patients, correct?

14 A I'd have to look at the exhibit again.

15 Q Okay.

16 MR. REICH: Sean, if you could pull it
17 up. It's Exhibit 1163, please.

18 And it should be already in the folder,
19 Dave, or the chat box, whichever you have access
20 to.

21 MR. ANSTAETT: Okay. I'll let you know
22 when I have it.

1 Okay. I have it.

2 MR. REICH: Sorry, Sean. 1163.

3 PLANET DEPOS TECHNICIAN: My apologies,
4 Counsel. Stand by.

5 Exhibit 1163 is up.

6 MR. REICH: Okay. And if you could
7 scroll down to the abstract, please. And if you
8 see right after methods, Dr. Coca, it says "17
9 healthy male subjects were enrolled."

10 Do you see that?

11 A I see that.

12 Q Do you agree that this study was in
13 healthy male subjects?

14 A Yes.

15 Q And if you look at the conclusion, do
16 you see the last sentence that says "This
17 hypothesis needs to be confirmed by other
18 studies"?

19 A I see that.

20 Q Did you mention that in paragraph 81?

21 MR. ANSTAETT: Objection. Form.

22 A No, I didn't mention it.

1 Q And if we could go back to your report,
2 paragraph 82, page 41.

3 You state "In 2007, additional animal
4 studies were reported."

5 Do you see that?

6 A Yes, I see that.

7 Q Are the additional animal studies
8 you're referring to the exhibits in paragraphs 82,
9 83, and 84, which are exhibits 1150, 1151, and
10 1152?

11 A Yes.

12 Q And you'd agree those were each studies
13 in rodents, whether they be mice or rats?

14 A Yes, that's why it was characterized as
15 animal studies.

16 Q Okay. You have no reason to dispute
17 that they were in rodents?

18 A No reason.

19 Q Do you recall citing any animal studies
20 that were anything but rodents? I'm happy to have
21 you look and confirm, but I will represent to you
22 these were two rat studies and a mouse study.

1 A I agree.

2 Q And in paragraph 82 you note that
3 Exhibit 1150 was on an exendin-4 molecule; is that
4 right?

5 A Correct.

6 Q And in paragraph 83, you note that it
7 was molecule AC3174, which is similar to
8 exenatide.

9 Do you see that?

10 A I see that.

11 Q So it would be another exendin-4
12 analogue, right?

13 A Correct.

14 Q And in paragraph 84, that it was shown
15 that exenatide exerts those renal-protective
16 effects.

17 Do you see that?

18 A I see that.

19 Q So you'd agree that those three
20 exhibits were each animal studies focused on
21 exendin-4 analogs?

22 A Agree.

1 Q In your opinion, if a therapy reduces
2 blood pressure, blood glucose, or albuminuria, is
3 that therapy kidney-protective?

4 MR. ANSTAETT: Objection. Form.

5 A It can build the picture out that it is
6 likely kidney-protective.

7 Q So to confirm, without knowing anything
8 else, other than it reduces one of those three
9 risk factors, you would conclude that it's likely
10 kidney-protective?

11 MR. ANSTAETT: Objection to form.

12 You can answer.

13 A I'm sorry. No, I would say, if you
14 show all three, you're much more likely that you
15 have a kidney -- that you are dealing with a
16 kidney-protective therapy.

17 If you only have one of the three, then
18 it is not necessarily true. And there are
19 examples of where an agent could modify one of
20 those risk factors, yet, not be kidney protective.

21 Q Is reducing blood glucose
22 kidney-protective?

1 MR. ANSTAETT: Objection to form.

2 A It's a nuanced question, Josh. It can
3 be. It's certainly -- it's neither necessary nor
4 sufficient, let me put it that way. And I can
5 give examples where it doesn't always translate
6 into kidney protection.

7 Q If a therapy reduces blood pressure,
8 blood glucose, and albuminuria, is it
9 automatically kidney-protective?

10 MR. ANSTAETT: Objection to the form of
11 the question.

12 A I don't like the word "automatically."
13 But your pretest probability, now that
14 you're working on that -- on -- you're showing
15 multiple lines of the mediators of kidney disease,
16 or these intermediate-type outcomes, these softer
17 clinical end points, you're much more likely to
18 have a kidney-protective agent in hand when you've
19 shown all three to go in the correct direction.

20 Q What do you mean by "pretest
21 probability"?

22 A Well, in any given patient, you don't

1 know whether the drug you're administering will
2 ultimately prevent progression of their kidney
3 disease, right? We extrapolate a lot when we
4 treat patients, not only from, again, from all of
5 this, the whole story, the animal data, the early
6 data, the effects on the intermediate end points,
7 the large clinical trials. And then when you try
8 to apply this whole compendium of data to an
9 individual, whereas, we know there's a -- there's
10 responders and not responders that you can only
11 know after the fact, after, actually, for kidney
12 disease, sometimes many years have passed. There
13 is -- you can have a partial response. It's tough
14 to ascertain response, and this is an area of
15 active investigation, is how do you earlier assess
16 beneficial responses when initiating various
17 potential renal-protective agents?

18 So that's where the nuance comes in.

19 Does that answer the question?

20 Q Maybe. I'll have to think about it.

21 If you could turn to paragraphs 89 and
22 90 of your report. Actually, if you turn back to

1 paragraph 86 first.

2 A Sure.

3 Q Is paragraphs 86 through 89 your words?

4 MR. ANSTAETT: Objection to form.

5 A Yes.

6 Q So if we could turn to paragraph 89 and
7 90. And here you are providing some opinions
8 about liraglutide; is that correct?

9 A Correct.

10 (Coca Exhibit 7 marked for
11 identification and attached to the transcript.)

12 Q And you first point to Exhibit 1156,
13 and you note that this study found "No safety
14 concerns regarding use of liraglutide in patients
15 with renal impairment."

16 Do you see that?

17 A I see that.

18 Q Do you agree that Exhibit 1156, the
19 Jacobsen study, was a safety study?

20 MR. ANSTAETT: Objection to form.

21 A Well, this is a PK study of liraglutide
22 and, typically, PK studies are more about safety

1 than efficacy.

2 Q And their conclusion was, as you
3 phrased it, liraglutide could be safely
4 administered to CKD patients at the approved
5 doses.

6 Do you see that?

7 A I see that.

8 Q And that was a 2011 article? The --
9 sorry, wrong date -- strike that.

10 That was a 2009 article.

11 MR. ANSTAETT: I'm sure we can
12 determine that by looking at the article.

13 MR. REICH: Counsel, he can answer the
14 question.

15 MR. ANSTAETT: It's not a memory test,
16 Josh.

17 MR. REICH: No, it's not, but he can
18 answer -- Dave, Dave, your coaching is not proper.

19 MR. ANSTAETT: I'm not coaching. It's
20 ridiculous.

21 MR. REICH: Yes, it is.

22 MR. ANSTAETT: Show him the article.

1 BY MR. REICH:

2 Q Answer the question.

3 A Can you show me the article, Josh?

4 Q Yes.

5 MR. REICH: Sean, can you share the
6 article with him?

7 PLANET DEPOS TECHNICIAN: That would be
8 1156, Counsel?

9 MR. REICH: Yes, sir.

10 PLANET DEPOS TECHNICIAN: Exhibit 1156
11 is up.

12 Q And do you see, in the bottom right or
13 the top right indications, middle right, that it
14 was accepted in 2009?

15 A 2009.

16 Q And if you scroll down to the middle of
17 the first page, under conclusions, you'll see it
18 states "This study indicated no safety concerns
19 regarding the use of liraglutide in patients with
20 renal impairment."

21 Do you see that?

22 A I see that.

1 Q And it notes "There is, however,
2 currently limited experience with liraglutide in
3 patients beyond mild-stage renal disease."

4 Do you see that?

5 A I see that.

6 Q And are you aware, at this point,
7 whether liraglutide had already been in Phase II
8 and Phase III studies?

9 MR. ANSTAETT: Objection to form.

10 A I believe there -- the lead program, it
11 was the lead 1 through 6 trials that I think
12 were -- multiple were published in 2009. So they
13 were already in phase -- I guess those lead
14 programs were considered Phase II, I think.

15 Q And so, is it fair to say that even
16 after six of the lead trials were completed, or
17 near completed, there was still uncertainty as to
18 whether it would even be safe to administer
19 liraglutide to patients with mild renal
20 impairment?

21 MR. ANSTAETT: Objection to form.

22 A Depends on the inclusion criteria of

1 the lead trials, which I don't recall off the top
2 of my head, on where they excluded patients
3 with -- by GFR criteria.

4 Q What was the point of running the study
5 being discussed in Exhibit 1156 to confirm whether
6 it was safe to do so if they already -- you know
7 what -- strike that.

8 Dr. Coca, why would Novo run a clinical
9 trial to determine if it was safe to administer
10 liraglutide to patients with mild renal impairment
11 in 2009 if it was already known?

12 MR. ANSTAETT: Objection to form.
13 Objection. Foundation.

14 A I cannot get at the motivations of
15 Novo, but just because a study was published in
16 2009, A, I don't know when the patients were
17 actually enrolled and how long it took to be
18 published. But, B, people are always concerned
19 about clearance of -- I mean, the two major ways
20 drugs are cleared are kidney and liver, and
21 there's always concern about potential toxicity,
22 so it's always good to concern safety of these

1 agents in patients with kidney impairment.

2 Q And you agree, as of the date of this
3 publication, the author said there was limited
4 experience with liraglutide in patients beyond
5 mild-stage renal disease?

6 A At that time, I agree with the comment.

7 MR. REICH: If we could pull up
8 Exhibit 1157, please, Sean.

9 (Coca Exhibit 8 marked for
10 identification and attached to the transcript.)

11 MR. REICH: Actually, sorry, pull up
12 paragraph 90 of Exhibit 1306.

13 Q You see here that you start off
14 paragraph 90 with a meta-analysis of the Phase III
15 lead clinical trials was also published?

16 A I see that.

17 Q Does that refresh your recollection
18 that the lead trials were Phase III studies?

19 A Yes, it does.

20 Q And they were already published as of
21 the date Exhibit -- at least, of Exhibit 1157?

22 MR. ANSTAETT: Objection. Form.

1 A I don't know the exact timing, within
2 2009, the papers came out compared to the PK
3 study.

4 Q Yeah. I still think there might be
5 confusion. 1156 was 2009. But I will show you.

6 MR. REICH: Sean, if you could share
7 1157.

8 Q Dr. Coca, I might ask you some
9 questions on paragraph 90 and Exhibit 1157 at the
10 same time. You said you have your report in front
11 of you, correct?

12 A Yes, I do.

13 Q For clarity, we'll keep 1157 on the
14 screen. I'll have you look at your report, at
15 paragraph 90, fair?

16 A Fair.

17 Q So, for Exhibit 1157, you see it has a
18 copyright date of 2011?

19 A Yes, I see that.

20 Q And if you go to the abstract on the
21 first page, please.

22 Do you see that in the objective, it

1 says to "determine the effect of mild renal
2 impairment on the efficacy and safety of
3 liraglutide in patients with type 2 diabetes"?

4 A I see that.

5 Q And they're -- strike that.

6 You describe Exhibit -- in paragraph 90
7 you write, "Thus, by the priority date of the '462
8 patent, it was recognized that a 1.8-milligram
9 daily dose of liraglutide was safe for CKD
10 patients, and the data, in fact, indicated
11 liraglutide was effectively resulting in better
12 kidney outcomes, i.e., low rates of acute renal
13 failure and albuminuria."

14 Do you see that?

15 A I see that.

16 Q And was this exclusion based off
17 Exhibit 1157?

18 A Yes.

19 Q And you agree that the objective was
20 just to determine the efficacy and safety of
21 liraglutide in this patient population, correct?

22 A Right.

1 Q And the author's conclusion was mild
2 RI, as determined by the Cockcroft-Gault equation,
3 had no effect on the efficacy and safety of
4 liraglutide in this meta-analysis.

5 Do you see that?

6 A Yes, I see that.

7 Q And if we go to the page 9, the
8 conclusion section again. And I'll let you read
9 the conclusion.

10 Let me know when you're done.

11 A Okay. I read the conclusion.

12 Q Did the authors conclude that the data
13 indicated that liraglutide was effectively
14 resulting in better kidney outcomes?

15 A No, the word "better" is not -- is not
16 indicated there. Perhaps the statement should be
17 liraglutide is effectively resulting in low rates
18 of acute renal failure and albuminuria.

19 Q Sorry, to be clear, I wasn't saying
20 that that was a direct quote. I'm just wondering,
21 did the authors conclude that liraglutide resulted
22 in better kidney outcomes?

1 MR. ANSTAETT: Objection to form.

2 A No.

3 Q You'd agree with me that their
4 conclusion was that liraglutide was safe in
5 patients with type 2 diabetes and mild renal
6 impairment, correct?

7 A Correct.

8 Q And they expressly note that "Further
9 studies and more experience in patients with T2DM
10 and more advanced degrees of renal failure will
11 ultimately be required to better characterize the
12 efficacy and safety profile in this patient
13 population."

14 Do you agree with that?

15 A That's what they state, yes.

16 Q At this point, you have provided
17 opinions that as of 2011, everyone expected
18 liraglutide and GLP-1s, as a class, to actually
19 improve kidney outcomes in patients, correct?

20 MR. ANSTAETT: Objection to form.

21 A Well, when you combine a multitude of
22 animal studies, granted most in rodents, as we

1 discussed, with the fact that the lead trials were
2 not set up to examine long-term kidney outcomes or
3 any of the hard clinical outcomes, since I think
4 this was only, at most, six months of follow-up
5 and it's not sufficient to assess efficacy for
6 kidney outcomes, the fact that the lead program
7 did show consistent effects of liraglutide in
8 reducing blood glucose or hemoglobin A1C, body
9 weight, and blood pressure, again, builds out this
10 picture that along with that animal data and the
11 clinical trial data, that in a properly tested
12 cohort, how we're to assess a kidney outcome, a
13 high pretest probability that this class of agents
14 will protect the kidneys.

15 Q Did Novo have access to all the studies
16 you cited in your report as of 2011?

17 MR. ANSTAETT: Objection to form.
18 Objection. Foundation.

19 A I don't know what Novo had access to,
20 but these were data in the public domain.

21 Q And neither of these two liraglutide
22 studies concluded that liraglutide would likely

1 improve kidney outcomes, fair?

2 MR. ANSTAETT: Objection to form.

3 A These last two exhibits do not -- the
4 decade, the 2000s, and the few that I referenced,
5 did suggest that the GLP-1s could be a promising
6 therapy for kidney disease, given its properties
7 and findings in the animal models and the early
8 clinical trial data.

9 Q Sorry, I'm not sure if you froze for
10 everyone else, but you froze right in the middle
11 of that answer. If you could please -- hate to do
12 this to you, but if you could, please, repeat your
13 answer because I don't think anyone got it.

14 A Can you repeat the question?

15 Q I can. The last two exhibits -- I'm
16 sorry. Strike that.

17 Neither of the two liraglutide studies
18 that you cite concluded that liraglutide would
19 likely improve kidney outcomes, fair?

20 MR. ANSTAETT: Objection to form.

21 A I concur that these two -- last two
22 exhibits do not suggest that they would improve

1 kidney outcomes. But what I did state, when it
2 froze, was that expert reviews published prior to
3 2010, assessing, again, the totality of evidence
4 in the experimental animals in the early clinical
5 trials data are hopeful and suggestive of this
6 potential for kidney-protective effects of this
7 class of agents.

8 Q And are those expert reviews you're
9 discussing the ones you cited in paragraphs 77 to
10 84?

11 Let me withdraw that question.

12 Are you referring to anything not cited
13 in your declaration when you were talking about
14 the expert publications, the expert reviews?

15 A I'm just reviewing my list of exhibits
16 here.

17 Paragraphs I -- paragraphs -- I'm
18 referring to the articles by Knudsen,
19 Exhibits 1031 to 1033, particularly, the 1033 one
20 by Knudsen on liraglutide, I think, was pretty
21 comprehensive in summarizing the combination of
22 the animal plus clinical data that I'm referring

1 to.

2 Q Are you aware -- you had discussed
3 exendin-4 in some of the paragraphs we had
4 discussed previously, paragraph 77 to 84.

5 Do you recall that?

6 A Yes.

7 Q Are you aware that there were concerns
8 about using exenatide, in 2009 and 2010, in
9 patients with severe renal impairment or end-stage
10 renal disease?

11 MR. ANSTAETT: Objection to form.

12 A With specifics on exenatide, I'm not
13 sure. But the liraglutide data seems to be
14 alleviating the concern, at least for --
15 alleviating the concerns in patients with advanced
16 kidney disease, or some degree of CKD.

17 Q Would you be surprised if it was
18 recommended that liraglutide not be administered
19 in patients with renal impairment?

20 MR. ANSTAETT: Objection to form.

21 A In the label or in the literature?

22 Q Either.

1 A I don't recall all the details on
2 liraglutide in advanced kidney disease.

3 It's also helpful to -- these are kind
4 of vague terms, it's helpful to use eGFR
5 delineations for where we prescribed these
6 medications. For example, I vividly remember,
7 only a few years ago, SGLT2s were thought to be --
8 were restricted in those with eGFR below 60 or
9 below 45.

10 And then, as the additional evidence
11 kept coming out and they kept pushing the
12 inclusion criteria and opening up the exclusion
13 criteria for these trials, those initial concerns
14 were alleviated and completely abated, as they
15 showed the protection of SGLT2 inhibitors. And
16 now we have data all the way down to eGFR --
17 enrollment of eGFR greater than 20 and data on
18 them that they even need not be discontinued, even
19 if patients progress to dialysis.

20 So that's a way people, initially, are
21 narrow and concerned about safety, and as efficacy
22 data comes in, then the boundaries get opened up

1 to see how many patients can be included and where
2 they can be included, regardless of their kidney
3 function.

4 Q Okay. But would you be surprised if,
5 in 2010, there was a recommendation for using
6 liraglutide in patients with renal impairment with
7 caution to proceed with caution in that patient
8 population?

9 MR. ANSTAETT: Objection to form.

10 A Renal impairment is not synonymous with
11 chronic kidney disease nor diabetic kidney disease
12 because, for example, many patients that are
13 recommended -- that are classified as DKD and that
14 meet inclusion to be treated with GLP-1 receptor
15 agonists, as per the latest guidelines, actually
16 have no renal impairment, their eGFR can be above
17 60, but they have albuminuria, which satisfies the
18 criteria for having diabetic kidney disease, given
19 they have kidney damage.

20 So renal impairment is a clearance
21 issue; diabetic kidney disease does not always
22 mean renal impairment. There can be just that

1 kidney damages through albuminuria. So it's two
2 different concepts.

3 Q So statements about impact on renal
4 impairment are not relevant to chronic kidney
5 disease.

6 Is that what you're saying?

7 MR. ANSTAETT: Objection to form.

8 A Not all CKD have renal impairment, is
9 my point. There's about half the patients with
10 diabetic kidney disease have no renal impairment
11 and, rather, they have just evidence of
12 albuminuria, a high uACR.

13 And that's certainly a population that
14 would not be contraindicated from receiving GLP-1
15 receptor agonists, even in the nascent times, when
16 as the evidence was still emerging in the 2000s.

17 Q So about half the patients with
18 diabetic kidney disease do have renal impairment?

19 A Yeah, I'm just using the line of an
20 eGFR above and below 60 as that criterion to
21 say -- again, renal impairment is a very outdated
22 term that we really don't use anymore because now

1 it should be defined. Are you referring --
2 National Kidney Foundation actually has the CGA
3 criteria cause GFR and albuminuria, so we have the
4 five stages of GFR, stages 1 through 5, and
5 there's three stages of albuminuria, A1, A2, A3.

6 Q So, to circle back to my question,
7 would it surprise you, at all, if there was
8 caution recommended for administering liraglutide
9 to patients with renal impairment?

10 MR. ANSTAETT: Objection to form.
11 Asked and answered.

12 A I guess it would not be surprising
13 about renal impairment, since that can -- implies
14 low clearance, but it's only a subset of CKD or
15 DKD.

16 Q And if it's in a therapy, like
17 liraglutide, which was indicated for type 2
18 diabetes, all the patients would have type 2
19 diabetes, correct?

20 MR. ANSTAETT: Objection to form.
21 Foundation.

22 A They would have type 2 diabetes but

1 they -- only a fraction would have renal
2 impairment.

3 Q Would such a caution be relevant to
4 your expectation, as of 2010, on the effects of
5 the kidney?

6 MR. ANSTAETT: Objection to form.

7 A Again, you could have a
8 kidney-protective drug that works on the early
9 stage of disease before there's renal impairment.
10 So just because there's caution on toxicity, or
11 side effects of an agent and those with renal
12 impairment does not mean it cannot be
13 kidney-protective. The two are mutually
14 exclusive.

15 And it doesn't even mean that the
16 toxicity of GLP-1 with renal impairment would be
17 kidney related. It could be kidney, it could be
18 non-kidney. So all of this has to be specified
19 and kept separate, efficacy versus safety and
20 which organs it protects versus not protects or
21 injures or not injures.

22 Q Is this a factor you would have

1 considered in 2010?

2 MR. ANSTAETT: Objection to form.

3 A In 2010, it's -- I could still make the
4 hypothesis, given all those animal studies we
5 reviewed together and outlined in my declaration,
6 as well as the effects of liraglutide on glucose
7 control, blood pressure, and weight to suggest
8 that this class of agent would have
9 kidney-protective events -- effects and for which
10 subset of DKD remains to be determined. But,
11 again, that's a -- see, kidney stage is a nuance
12 here that's not being addressed.

13 Q Can you turn to paragraph 94 of your
14 report, please.

15 A Yeah.

16 Q Are you there?

17 A I got it. Yes.

18 Q You write, "I understand there were no
19 publicly available data resulting from use of that
20 dose at the time."

21 And you were referring to the
22 .8-milligram dose.

1 Do you see that?

2 A I see that.

3 MR. ANSTAETT: Just so the record's
4 clear, you're referring to semaglutide, since
5 we've been talking about liraglutide, right?

6 MR. REICH: Correct. Thanks, Dave.

7 Q For the record, there was no publicly
8 available data resulting from use of the
9 .8-milligram dose of semaglutide, as of 2010,
10 correct?

11 A Correct.

12 Q Okay. So you agree there would be no
13 evidence of how .8 milligrams of semaglutide would
14 perform as of 2010, correct?

15 MR. ANSTAETT: Objection -- sorry,
16 didn't mean to interrupt. Objection to form.

17 A I think it's, I agree, clearly stated,
18 there was no data of how .8-milligram dose of
19 semaglutide would perform.

20 Q Do you understand whether there was
21 publicly available data as to how any dose of
22 semaglutide would perform as of 2010?

1 MR. ANSTAETT: Objection to form.

2 A Not that I'm aware of.

3 Q So then you would agree there was no
4 publicly known dose response curve for
5 semaglutide, correct?

6 MR. ANSTAETT: Objection to form.

7 A At that time?

8 Q As of 2010?

9 A Yeah, not at that time.

10 Q And true as of -- would any of your
11 answers change if I set the date to 2012?

12 MR. ANSTAETT: Objection to form.

13 A I believe the answer is still the same.

14 Q Okay. So to be clear, as of 2012,
15 there was no known data for any dose of
16 semaglutide, correct?

17 MR. ANSTAETT: Objection to form.

18 You can answer.

19 A Not that I'm aware of.

20 Q You understand that unexpected results
21 are based on the expectation as of the priority
22 date?

1 A Yes.

2 Q How is it, Dr. Coca, that you would
3 expect 1.0 milligrams of semaglutide to behave in
4 a particular way if you had no evidence, at all,
5 of how semaglutide behaved at any dose, let alone
6 .8?

7 MR. ANSTAETT: Objection to form.

8 A Again, the dose -- my presumption would
9 be based upon, again, the class effect and the
10 clinical data -- the class effect of GLP-1s in
11 animals and the clinical data seen from the other
12 GLP-1s, particularly the liraglutide.

13 Q So, in your opinion, it was expected
14 based on -- well, I'll withdraw that question.

15 One sec.

16 Can you turn to paragraph -- oh, yeah.

17 MR. REICH: Dave, now probably is a
18 good time for a break.

19 MR. ANSTAETT: Okay. Five minutes?

20 MR. REICH: Ten minutes, please.

21 MR. ANSTAETT: Okay.

22 (Recess taken from 1:25 p.m. to

1 1:38 p.m.)

2 BY MR. REICH:

3 Q Dr. Coca, I think previously you had
4 agreed that albuminuria is a surrogate endpoint
5 for kidney health.

6 Do you recall that?

7 A Yes.

8 Q Have you ever heard of the Archives of
9 Internal Medicine?

10 A Of course.

11 Q Is it a reputable source?

12 A Yes. And they changed their names to
13 JAMA Internal Medicine, probably over a decade ago
14 now.

15 Q Have you ever published in the Archives
16 of Internal Medicine when it was still called the
17 Archives of Internal Medicine?

18 A Yes.

19 Q Have you ever heard of the article
20 "Role of Intensive Glucose Control and Development
21 of Renal end points in Type 2 Diabetes:
22 Systematic Review and Meta-Analysis"?

1 A Yes.

2 MR. REICH: Sean, if you can display
3 what has been marked as Exhibit 2603, I would like
4 to introduce it.

5 (Coca Exhibit 9 marked for
6 identification and attached to the transcript.)

7 MR. ANSTAETT: And just for -- sorry.
8 Didn't mean to interrupt, Sean.

9 Just for the record, this is a new
10 exhibit that previously has not been admitted in
11 this proceeding and, so, we reserve on our right
12 to lodge objections to it.

13 PLANET DEPOS TECHNICIAN: Exhibit 2603
14 is up.

15 Q Is this an article you're the lead
16 author on?

17 A Yes.

18 Q And if you scroll down, do you see it's
19 dated May 28th, 2012?

20 A Yes.

21 Q Have you ever made any corrections to
22 this article, that you're aware of?

1 A No, I did not make any corrections.

2 Q Is there anything you wrote in this
3 that you think is wrong or thought was wrong at
4 the time?

5 MR. ANSTAETT: Objection to form.

6 A Well, the point estimate, for instance,
7 kidney disease, trended towards significant, but
8 the upper bound of that 95 percent compensable did
9 cross 1. And while a purest can state there's no
10 obvious effect, the wisdom I've obtained over the
11 last, I guess, now, 12 years since writing this
12 paper, is that a non-statistically significant
13 effect is not equal to a null effect, and that a
14 non-statistically significant effect could be due
15 to low power to ascertain that outcome and that to
16 truly conclude something as null, you need a tight
17 confidence interval around the point estimate of
18 1. And in general, that would be .9 to 1.1, or .8
19 to 1.2, to really suggest that there was no effect
20 and, thus, that is one -- I don't know if I want
21 to call it regret. But a nuance I wish I had more
22 properly delineated in this manuscript.

1 I think we did refer to the low power
2 may have obscured the ability to detect the
3 effect. So, I think that answers your question.

4 Q This was your view at the time,
5 correct?

6 MR. ANSTAETT: Objection to form.

7 A What was my view at the time, what you
8 just stated or are you pointing to something else
9 on the --

10 Q This article, the words reflect your
11 view as of the date of the article, correct?

12 A Correct.

13 Q And your conclusion was intensive
14 glucose control reduces the risk for
15 microalbuminuria and macroalbuminuria but evidence
16 was lacking that intensive glycemic control
17 reduces the risk for significant clinical and
18 renal outcomes, such as doubling of the serum
19 creatinine level, ESRD, or death from renal
20 disease during the years of follow-up of the
21 trials.

22 Do you see that?

1 A Wait, can we scroll a little? I --

2 MR. ANSTAETT: Yeah, where are you
3 looking, Josh?

4 Q Sorry. I thought he was on the first
5 page. Conclusions. Scroll down. Conclusions.

6 A Yeah, so in this -- I think I used the
7 phrase once before in this deposition. Absence of
8 evidence is not evidence of absence. So, I'm glad
9 I did use that nuance, then. It just says we
10 didn't have the evidence yet that one arm of --
11 one angle of treatment, and you asked me a
12 question about this earlier, that glycemic
13 control, in itself, isn't sufficient to prevent
14 the long-term hard clinical outcomes.

15 And like I was alluding to then, and
16 I'll reiterate now, it is one -- it's one
17 objective. It does not -- just achieving glycemic
18 control does not mean you will yield beneficial
19 outcomes, and the reasons are that if you achieve
20 that glycemic control with, for example, just
21 exogenous insulin administration, or another drug
22 class that was en vogue back in this -- a little

1 before this area, kind of weighing on the favor in
2 2007, 2018, the thiazolidinedione class for
3 treatment of diabetes, both of those -- insulin,
4 of course, and TZDs, as we call them, the
5 thiazolidinediones, improve glycemic control, but,
6 really, have not been shown to, in and of
7 themselves, to improve kidney or cardiovascular
8 outcomes.

9 In fact, the TZDs, because of their
10 effect on -- they cause sodium retention, so
11 they're associated with increased risk of heart
12 failure, they're also associated with increased
13 risk of myocardial infarction, they didn't really
14 cause weight loss. So that's an example of an
15 agent where glycemic control is better but
16 clinical outcomes were not better.

17 But then I also said that if you have a
18 triumvirate of beneficial directional responses,
19 glycemic control, better blood pressure, weight
20 loss, and let's put the fourth arm as an
21 improvement in albuminuria, then, because all
22 those things are going in the right direction,

1 it's much more likely that improvement of hard
2 clinical outcomes will be observed, both at an
3 individual level and at a trial level.

4 Q Turn to -- sorry.

5 A And one more thing, Josh, just now that
6 we have it up at the right place because I was
7 talking about that from memory. The ESRD points
8 estimate and confidence interval. The 0.69, with
9 a confidence interval of 0.46 to 1.05 for
10 end-stage kidney disease. So it's not
11 statistically significant, upper bound crosses 1,
12 like I mentioned. But, again, the nuance and the
13 wisdom I acquired in my epidemiologic thinking, a
14 few more patients or few more outcomes suggest
15 there's actually a third -- somewhere in the range
16 of a 31 percent risk reduction of end-stage kidney
17 disease with that .69, one minus .69 would be a
18 31 percent risk reduction, and it just missed
19 significance. Again, and I think I had it in the
20 results in the discussion, there was only about
21 2 percent event rate of ESRD, so that's a power
22 issue and not a reason to conclude that there's a

1 null effect of, in this case, intensive glucose
2 control, in and of itself.

3 Q But you agree that the stated
4 conclusions accurately state your view at the
5 time?

6 MR. ANSTAETT: Objection to form.

7 A I agree that the one aspect of just
8 controlling glucose alone, at the time, while
9 improving the intermediate surrogate outcome of
10 albuminuria, there was not sufficient evidence
11 that it improved the clinical outcomes.

12 Q Do you recall when exenatide was
13 approved?

14 A No, I don't recall.

15 Q Do you recall if it was before or after
16 2018?

17 A I don't recall.

18 MR. REICH: Sean, could you pull up
19 Exhibit 1021, please.

20 (Coca Exhibit 10 marked for
21 identification and attached to the transcript.)

22 PLANET DEPOS TECHNICIAN: Stand by.

1 Q Dr. Coca, do you have any reason to
2 disagree that Byetta was -- Dr. Coca, do you see,
3 top left, it says the initial U.S. approval for
4 Byetta exenatide was 2005?

5 A I see that.

6 Q Does that refresh your recollection
7 that Byetta was approved in the U.S. as of 2005?

8 A Yes.

9 MR. REICH: Can you go back to 2603,
10 please, Sean.

11 PLANET DEPOS TECHNICIAN: Did you say
12 2603, Counsel?

13 MR. REICH: Yep.

14 Q And if you scroll down to page 2,
15 Dr. Coca, on the left, there's a sentence
16 beginning "a recent study." It's at the very
17 bottom of that screen, right now. Oops, sorry.
18 Up a little. Right there. The top left.

19 "A recent study demonstrated that
20 despite substantial increases in the use of
21 glucose-lowering medications...from 1988 to 2018,
22 the per balance of CKD in individuals with

1 diabetes increased."

2 Do you see that?

3 MR. ANSTAETT: Yes, I see that.

4 Q That was after Byetta was on the market
5 and approved in the U.S.?

6 MR. ANSTAETT: Objection. Form.
7 Misstates the document.

8 A Just because Byetta was approved in
9 2005, I'm not sure about the market penetration it
10 had by the end of that follow-up period in 2008.

11 MR. REICH: Take this down.

12 Q Could you turn to paragraph 20 of your
13 report, Dr. Coca.

14 MR. ANSTAETT: Did you say 20, Josh?

15 MR. REICH: Yes. 20. Sorry.

16 Q Are you there?

17 A I'm there.

18 Q Is it your understanding that if a
19 property, such as the ability to reduce blood
20 glucose, was present in the prior art, that any
21 improvement in that property is just a difference
22 in degree?

1 MR. ANSTAETT: Objection to form.

2 A If you're saying would a greater
3 reduction in glucose represent a difference in
4 kind or degree?

5 Q My -- let me try my question.

6 Can a difference of degree be
7 significant enough that it is considered a
8 difference in kind?

9 MR. ANSTAETT: Objection to form.

10 A In general, I don't know where the --
11 where the threshold falls legally. A difference
12 in kind versus degree. But I would consider most
13 of the biological effects and differences, you
14 know, a certain amount of difference in whether
15 it's blood glucose, albuminuria, eGFR response,
16 risk components for positive outcomes, those kind
17 of differences largely represent differences in
18 degree and not differences in kind.

19 I mean, if -- again, I don't know if
20 you have -- if something is a 10 percent
21 difference and another thing is a 99 percent
22 difference or whatever, something like that, does

1 it reach the difference in kind? I'm not sure,
2 but, generally, I think a difference in kind as
3 something not having an effect versus a different
4 agent having -- having a protective effect.

5 Q Did you consider whether the magnitude
6 of increase here and the properties of semaglutide
7 was unexpected in such a way that it rendered the
8 changes a difference in kind?

9 MR. ANSTAETT: Objection to form.

10 A Yes, I did consider that. And I felt
11 that semaglutide represents a difference, if any,
12 a difference in degree on kidney outcomes.

13 Q But you don't know where the legal
14 threshold is for what differentiates between a
15 difference in the grade versus the difference in
16 kind; is that correct?

17 MR. ANSTAETT: Objection. To form.

18 A Correct, I don't know the legal
19 definition, but I can say confidentiality say, for
20 example, data published post priority date, as one
21 of the exhibits in the Shaman (phonetic) article
22 comparing effects of dose -- different doses of

1 semaglutide with liraglutide 1.8-milligram
2 represent -- I can comfortably state those
3 differences on albuminuria and eGFR on differences
4 in degree.

5 Q Do you understand whether more than one
6 invention can have unexpected results?

7 MR. ANSTAETT: Objection to form.

8 A Can more than one invention have
9 unexpected results?

10 Q Yeah.

11 MR. ANSTAETT: I'm sorry. I didn't
12 mean to interrupt.

13 A I'm not a -- I'm not a patent lawyer.
14 I don't know.

15 Q You refer to a later file patent
16 application in your declaration;

17 Do you recall that?

18 A Yes.

19 Q So is it your understanding that a
20 later-filed patent application prevents there from
21 being any unexpected results that are attributable
22 to the '462 patent at issue here?

1 MR. ANSTAETT: Objection to form.

2 A I'm not an attorney. I don't know what
3 the law states on that.

4 Q Do you understand whether there can be
5 nexus to more than one patent?

6 MR. ANSTAETT: Objection to form.

7 A Again, with the caveats I -- the
8 legalese here is not my strength. I don't know
9 about the multiple patent -- nexus rules.

10 Q On page 56 of your declaration, you
11 have an entire section entitled "a later-filed
12 patent application demonstrates there's no nexus
13 between the claims of the '462 patent and the
14 kidney-protective effects of semaglutide."

15 Do you see that?

16 A I see that.

17 Q So in this section, where you provide
18 opinions based on the later-filed patent
19 application, did you understand that the mere
20 existence of that later-filed patent application,
21 meant there could be no nexus to the '462?

22 MR. ANSTAETT: Objection to form.

1 A Again, as in my role here as a
2 physician expert, it does seem to me that a newly
3 filed patent, now trying to claim -- claim the
4 methods of reducing the events that were not
5 claimed would suggest that the prior patent did
6 not cover it. But that's -- that's what I
7 understand.

8 Q But you don't know one way or the
9 other?

10 MR. ANSTAETT: Objection to form.

11 A Well, as I state, it's in my opinion,
12 from what I understand about nexus and law, that
13 this new patent filing would suggest there wasn't
14 a nexus, or else, why would -- why would a new
15 patent have needed to be filed? But that's my
16 understanding.

17 Q In paragraph 115 you note that those
18 are the current claims that have those particular
19 features or the claims that are currently pending;
20 is that correct?

21 A What's the key word you have, currently
22 pending, current?

1 Q Yeah.

2 A I presume that to be accurate, but I'm
3 not aware if that's changed.

4 Q In the second sentence, it also states
5 that it currently has claims directed to methods,
6 correct?

7 A Yes. Yes. That's what it states,
8 yeah.

9 Q And you understand those claims may
10 change, correct?

11 A Yeah.

12 Q You also provide some opinions that
13 there's no nexus because chronic kidney disease is
14 not specifically identified in the claims, are not
15 discussed in the specification of the '462.

16 Do you recall those opinions?

17 A Yes.

18 Q Is it your understanding that chronic
19 kidney disease has to be discussed in the
20 specification for there to be unexpected results
21 for the claims of the '462 patent?

22 MR. ANSTAETT: Objection to form.

1 A It's my understanding that it doesn't
2 have to be explicitly stated. But the fact is it
3 wasn't stated, but -- but not that it has to be
4 stated.

5 Q And you focus a lot, in your opinions,
6 on whether 1.0-milligram is responsible for the
7 effects, the kidney-protective effects of the
8 claim.

9 Do you recall those?

10 A Yes.

11 Q Is it your understanding that
12 1.0 milligrams of semaglutide has to be solely
13 responsible for all of the unexpected results of
14 the claim for there to be nexus?

15 MR. ANSTAETT: Objection to form.

16 A I'm not sure. But I know that, for
17 example, liraglutide, 1.8 milligrams, provides a
18 similar, maybe slightly difference of degree on
19 kidney -- on intermediate kidney outcomes. And I
20 know that, again, postdoc analyses have
21 demonstrated this, from, like, the sustained 6
22 trial, you know, .5 milligrams of semaglutide also

1 improved -- has some benefits for kidney outcomes
2 and kidney function, as does higher doses of
3 semaglutide, 2.4-milligram. So I don't see any --
4 1.0-milligram dose of semaglutide is the only
5 kidney-protective dose of semaglutide or of other
6 GLP-1 receptor agonists.

7 Q Is it your understanding, for there to
8 be a nexus, that it has to be the only dose, the
9 1.0-milligram dose has to be the only dose that
10 provides those kidney-protective effects?

11 MR. ANSTAETT: Objection to form.

12 A I'm not sure how heavily the law
13 requires it to be the 1.0-milligram dose. But,
14 again, as providing my testimony as a physician, I
15 see the differences between different doses of
16 semaglutide or the GLP-1 receptor antagonist's
17 difference in degree.

18 Q When you were coming to your opinions
19 as they relate to nexus, was it your understanding
20 that you should look to the claim, as a whole,
21 rather than focus on only 1.0 milligrams?

22 MR. ANSTAETT: Objection to form.

1 A I think I did both, focused on the 1.0
2 and the claims as a whole.

3 Q Did you consider whether any of the
4 unexpected results are due to the once-weekly
5 administration of semaglutide?

6 MR. ANSTAETT: Objection to form.

7 A Well, insofar as I think closer -- some
8 of the closest prior art is also related to the
9 1.8-milligram dose of liraglutide, which is once
10 daily, and so that once weekly is not the
11 completely necessary timing of administration, as
12 well as I'm -- you know, I pointed out in
13 declaration, there is also oral dosing of
14 semaglutide on a daily basis that may also have
15 provided kidney benefit.

16 So, again, the once weekly versus other
17 timings is not a completely vital aspect to this.

18 Just a second.

19 Q The kidney-protective properties that
20 you consider to be known in the art, as of the
21 invention date, are those the properties discussed
22 in Section 7C that we had gone through earlier

1 today?

2 MR. ANSTAETT: Objection to form.

3 A 7C is page -- is it the animal studies?

4 Those with the cites -- that part,
5 again, outlined potential direct effects of GLP-1
6 and some kidney. There are other parts in my
7 declaration that talk about the indirect benefits
8 of GLP-1 on the kidneys because, again, those
9 multiple clinical aspects of glycemic control,
10 blood pressure, weight loss, are all important
11 risk factors that contribute to kidney disease if
12 not mitigated and improvements in those factors,
13 in most cases, would provide long-term kidney
14 protection.

15 Q To be clear, you said potential direct
16 effect, correct?

17 A From the animal phase? Again, I'd
18 never -- it's one piece of the multi- -- of the
19 puzzle, in terms of how GLP-1s are protecting the
20 kidneys, and I don't think anyone has worked out,
21 even now that the FLOW trial is conducted and
22 completed, what proportion of effect of GLP-1

1 receptor antagonists on kidney outcomes are
2 mediated by indirect versus direct effect. I
3 don't think any expert knows, and I think there's
4 going to be a lot more investigations around that,
5 but it's impossible to say at this time.

6 Q And you raised the FLOW manuscript, so
7 I think now is a good time to switch to it.

8 MR. REICH: Sean, can we pull up
9 Exhibit 2604, please.

10 (Coca Exhibit 11 marked for
11 identification and attached to the transcript.)

12 Q Dr. Coca, earlier we had discussed this
13 was published in the New England Journal of
14 Medicine, correct?

15 A Yes.

16 Q That's a reputable journal?

17 A Yes.

18 MR. ANSTAETT: Josh, give me just one
19 second. Sorry, which location are you referring
20 to?

21 MR. REICH: Perkovic 2604, I emailed
22 you.

1 MR. ANSTAETT: Okay. Just give me a
2 second to get it up. And as we discussed, because
3 this is a new exhibit that hasn't been in the
4 proceedings before, we're going to reserve our
5 right to raise objections to it. So I just have
6 to find your email again and tie it to the email
7 that's coming in. I've got it. That's fine.
8 I've got it.

9 Q Dr. Coca, are you familiar with Vlado
10 Perkovic?

11 A Yes.

12 Q Respected scientist in the field.

13 A Yes.

14 Q Same with Dr. Katherine Tuttle?

15 A Yes.

16 Q Dr. Bakris?

17 A Yes.

18 Q Fair to say that these are some of the
19 foremost experts in nephrology?

20 MR. ANSTAETT: Objection to form.

21 A They're all experts in nephrology,
22 correct.

1 Q And is the New England Journal of
2 Medicine a peer-reviewed journal?

3 A Yes.

4 Q Also reviewed by experts in the field?

5 A Yes.

6 Q And in the background, do you see where
7 it says, it's the second sentence, "Whether
8 treatment with semaglutide would mitigate these
9 risks is unknown," and it's referring to the risk
10 for kidney failure, cardiovascular events, and
11 death?

12 A I see that.

13 Q Do you agree with that statement?

14 MR. ANSTAETT: Objection to form.

15 A It's the standard end of the
16 introduction, otherwise, people would say, why did
17 you do the study?

18 Q Well, why did they go through the
19 effort to do this study if it was known that
20 semaglutide would have kidney-protective effects?

21 MR. ANSTAETT: Objection to form and
22 foundation.

1 A Again, I'm Novo -- a representative of
2 Novo, but I would say that to get regulatory
3 approval in the United States, and reliable, you
4 need to do a dedicated registered trial to get
5 approval for that given indication. And, again,
6 all the prior data of GLP-1 in -- and the presumed
7 protective effect, were garnered from the animal
8 studies we outlined, the clinical data on the
9 other agents, on these intermediate kidney
10 outcomes, or intermediate risk factors for kidney
11 outcomes as well, and the only way a regulatory
12 body would accept and give the label for DKD would
13 be to a dedicated trial such as this.

14 That being said, again, the design
15 paper weighed heavily on the totality of data and
16 gave excellent foresight and probabilities that
17 this would work. Meta-analyses of GLP-1 RAs
18 across different agents have shown consistently,
19 prior to the FLOW trial conduction and
20 publication, that they reduce cardiovascular
21 events and they improve albuminuria end points
22 consistently. And, thus, again, I think Novo went

1 in, smartly, with a good, you know, a good
2 bet -- good pretest probability that this would be
3 a positive trial, given everything I've just
4 outlined, so.

5 Q You disagree with that statement, you
6 think it was known that semaglutide would mitigate
7 these risks and Novo was just checking a box?

8 MR. ANSTAETT: Objection to form.

9 A It's not a pure counterfactual.
10 It's -- I mean, they could have -- they're not
11 going to write, we think this will work, but we
12 need to do -- no, this is part of the -- it's not
13 the grantsmanship, it's the -- it's the -- not the
14 game of publication. It's the -- it's the way we
15 phrase these things when we conduct studies.
16 You've got to leave some equipoise out there to
17 say -- it's just the way -- it's the way the
18 system works. You say, we need to investigate
19 further.

20 Q And the proof, you say, that suggests
21 semaglutide would work is based on the set of
22 articles we discussed earlier today?

1 MR. ANSTAETT: Object to form.

2 A I wouldn't use the word "proof."

3 I would say the probability that FLOW
4 is going to be positive using semaglutide was
5 high, the pretest possibility, because of
6 everything we've discussed today. We know that
7 there was protective effects in the animals. We
8 know that they reduced -- they not only improved
9 glycemic control, which I've said now multiple
10 times, alone is just not necessarily enough, but
11 they reduce weight, blood pressure, albuminuria,
12 so this was a good -- a good place to put your
13 chip down and say, "let's study it in a dedicated
14 trial that will satisfy the regulators because of
15 that pretest probability."

16 And the design paper that Rossing and
17 Bakris and others were on, discussed the totality
18 of evidence, largely as a class effect, they
19 pulled data from GLP-1s as a class effect, and
20 even their own words, in discussion, again,
21 largely suggest this will not be a unique effect
22 of semaglutide, again, in the discussions of this

1 very paper.

2 Q Dr. Coca, when was that design paper
3 written? You'd agree it was well after 2012,
4 right?

5 A Yes. It was written and published
6 after 2012, yeah.

7 Q And you said the pretest probability
8 would be high.

9 Do you recall that?

10 A Yes.

11 Q Would that be high as of 2012 or are
12 you basing that statement off of developments
13 between 2012 and the design paper for the FLOW
14 trial?

15 A Pretest probability is a continuum,
16 right?

17 And as more time accrues, more evidence
18 accrues, that number can move. It's not a
19 dichotomous yes/no. And, again, I wasn't -- I
20 wasn't focused on this very question in 2010 or
21 2012. But if somebody laid out all the data to
22 me, as we've done now, and said, look, in animal

1 models, you get more natriuresis, there's
2 antiinflammatory effects, you reduce glomerular
3 sclerosis, tubular interstitial fibrosis, your
4 blood pressure is better, you get less
5 albuminuria, and then the clinical data suggests,
6 from many of the agents, you're going to have
7 better glycemic control, lose weight. Again,
8 insulin doesn't cause you to lose weight, but
9 GLP-1s do, and you're going to get better blood
10 pressure clinically, it would have to go against
11 the tide to say, well, damn, if someone actually
12 did this study properly with a -- well, good
13 design, large sample size, it would have surprised
14 me if it wasn't positive. Even if this is -- I'm
15 putting myself in a time warp back to 2010.
16 Because it just would have had to all fall on the
17 face.

18 And granted, you could, then, have a
19 negative trial even because of trial design and
20 not because of biology. I would say, the
21 momentum, in terms of potential biological effect,
22 was tipped in the favor of kidney protection.

1 Q And out of everything you've just
2 listed, all the factors that would lead you to
3 that conclusion, you did not mention any of the
4 contradictory results discussed in the articles
5 you relied on, fair?

6 MR. ANSTAETT: Objection to form.

7 A Those few articles between 2002, with
8 the acute effects of GLP-1 peptide, infusion,
9 acutely increasing blood pressure, again, design,
10 infusion issues, this and that. By the late
11 2000s, you, then, saw there was enough Phase II,
12 Phase III data, again, from something similar to
13 liraglutide, that it's not certainly raising blood
14 pressure. So I think that would have mitigated
15 any concerns from the earlier 2000s.

16 Q The liraglutide data you're referring
17 to is the safety data we discussed earlier. Or
18 the lead trials published in 2009. And I think
19 there was a series of six of them, granted the
20 publication that summarized it all, it might have
21 been 2010, 2011 showed nicely, you know, the
22 consistent blood pressure reductions, the AIC

1 reductions, and weight loss across those studies,
2 so -- and, again, a nice contradiction to the TZD
3 study, the thiazolidinedione study, which was
4 giving the glycemic control thing without the
5 weight loss and blood pressure effect.

6 So --

7 MR. ANSTAETT: Can we get a check on
8 the time that we've been on the record?

9 MR. REICH: Can we go off the record
10 while we do that?

11 MR. ANSTAETT: Sure.

12 (Recess taken from 2:19 p.m. to
13 2:20 p.m.)

14 MR. REICH: Can we go back on and put
15 up Exhibit 24, please.

16 PLANET DEPOS TECHNICIAN: Stand by.

17 BY MR. REICH:

18 Q Dr. Coca, could you scroll down to the
19 conclusions, please. Sorry, on page 1, the
20 conclusions.

21 A Oh, the abstract conclusions?

22 MR. ANSTAETT: Are we on 2604?

1 MR. REICH: Yes, Dave.

2 A Semaglutide reduced the risk of
3 clinically important kidney outcomes from
4 cardiovascular causes -- kidney outcomes and death
5 from cardiovascular causes in patients with type 2
6 diabetes and chronic kidney disease.

7 Q That conclusion is limited to
8 semaglutide, fair?

9 A The headline conclusion, that is a
10 correct statement. Not incorrect at all. I will
11 not argue with it.

12 But the -- this is what I was referring
13 to before, is that -- is that in the discussion --
14 you've got to keep it concise for the New England
15 Journal, and appropriately so. You can't
16 overstate what the study states is found in the --
17 especially in the abstract, but they stated here,
18 and here is the implicit nod to what I'm saying,
19 clinicians and patients will need to consider the
20 order and priority of use for semaglutide (and
21 once-studied other GLP-1 receptor antagonists).

22 And I think what they're saying, again,

1 is now we have the evidence, hard evidence on
2 semaglutide, but they weren't expecting, again, if
3 you read all of the design paper, plus the
4 references of where they go through the mechanisms
5 of 20 to 23, where they say the effects -- let's
6 just go up, make sure we didn't miss anything
7 here. On the basis of experimental models, i.e.,
8 rodents, and biomarker data, the direct effects of
9 GLP-1 receptor antagonists, so now they're
10 counting them as a class, not semaglutide, on the
11 kidney, may include decreases in inflammation,
12 oxidative stress, and fibrosis, intrinsic kidney
13 and immune cells contain the GLP-1 receptor, and
14 GLP-1 receptor antagonist, again, class, not
15 semaglutide, reduce cellular expression of
16 pro-inflammatory and pro-fibrotic mediators,
17 references 20 to 23.

18 Reference 20 is called "Incretin Drugs
19 in Diabetic Kidney Disease: Biological Mechanisms
20 and Clinical Evidence."

21 Reference 21 is only with dulaglutide,
22 it's indicators of kidney fibrosis in patients

1 with type 2 diseases and chronic kidney disease
2 treated the dulaglutide.

3 Reference 22 is specific for
4 semaglutide, called "Nephro-protective Effects of
5 Semaglutide as Mono and Combination Treatment with
6 Lisinopril in a Mouse Model of Hypertension
7 Accelerated DKD."

8 And reference 23, again, an agnostic
9 paper on mechanisms and clinical application of
10 incretin therapies for diabetes and chronic kidney
11 disease.

12 So three out of the four references,
13 they use to support general statements on the
14 GLP-1 RA class and protect potential direct
15 effects, utilize some of that data, in totality,
16 that I've been repeatedly referring to, both from
17 the experimental animals and the previous clinical
18 data on numerous GLP-1 receptor agonists in
19 humans.

20 Q Dr. Coca, I'm trying to be very
21 respectful and let you finish your questions
22 [sic]. I asked you about the conclusion and

1 whether it was limited to semaglutide, and you
2 talked for four minutes, and we're on a time limit
3 here. So, normal --

4 MR. REICH: Dave, Dave, Dave.

5 MR. ANSTAETT: No, no, no.

6 MR. REICH: I'm letting him answer, I'm
7 just saying --

8 MR. ANSTAETT: And then you're telling
9 him he talked for four minutes. He's entitled to
10 answer the open-ended question you asked.

11 MR. REICH: I asked if --

12 MR. ANSTAETT: He does not have to
13 answer the question in the way you want.

14 MR. REICH: You're done. You're done.

15 MR. ANSTAETT: No, you're done.

16 MR. REICH: We only have 40 minutes.
17 I'll let you answer your stuff. You have redirect
18 with your lawyer, he can ask what he wants. We
19 only have 40 minutes. So, please, just try and
20 answer the question.

21 MR. ANSTAETT: Answer the question
22 whatever way you feel appropriate, Dr. Coca.

1 Q All those references you pointed to,
2 Dr. Coca, 21 to 24, is a single one, yes or no,
3 dated prior to 2012?

4 MR. ANSTAETT: Objection.

5 You can't instruct him how to answer a
6 question.

7 A The references are published after
8 2012, but they contain the data, some of which was
9 published before 2012.

10 Q Can you read that from this article,
11 yes or no? Does it tell you what they cite within
12 there? I'll withdraw the question.

13 Does a single reference, 21 to 24, in
14 the citations you just noted, provide any
15 information as to the date of the data that they
16 are basing their conclusions on?

17 MR. ANSTAETT: Objection to form.

18 A No.

19 Q And you referred to the "once studied"
20 language, if you want to scroll back up to that.

21 A To this part -- the once studied, yes?

22 Q Why do they need to be studied if, in

1 your opinion, it's known that they would work
2 to -- and have these kidney-protective effects?

3 MR. ANSTAETT: Objection to form.

4 A Well, because there's -- what this is
5 really getting to is a label indication. Now,
6 semaglutide will get the label for treatment of
7 DKD, so I think that's -- I think that's the
8 interpretation of what they're alluding to.

9 Q And all these statement are made in
10 May 2024, fair?

11 A Yes.

12 MR. ANSTAETT: Objection to form.

13 Q And if you turn to page 7 of the PDF,
14 right there. Do you see the sentence that states
15 the risk of death from any cause was 20 percent
16 lower in the semaglutide group than in the placebo
17 group?

18 Do you see that?

19 A I see that.

20 Q Is that a significant reduction, in
21 your opinion?

22 A Yes, it is.

1 Q Did you cite to anything, in your
2 declaration, that would indicate a reduction in
3 death due to GLP-1 administration?

4 MR. ANSTAETT: Objection to form.

5 A No, I was not asked to comment on death
6 and nor was -- nor was that data publicly
7 available at the time of my declaration.

8 Q Do you think that's an important
9 consideration now, to reduce mortality?

10 MR. ANSTAETT: Objection to form.

11 A An important consideration for use of
12 the drug?

13 Q And in rendering your opinions.

14 MR. ANSTAETT: Objection to form.

15 A Again, there have been multiple CVOT
16 trials of the various GLP-1 receptor antagonists
17 that have shown improvements in cardiovascular and
18 all-cause mortality. Again, this is the first one
19 in the dedicated DKD trial, but, it's not
20 surprising, let me put it that way, it's not
21 surprising.

22 Q Can you turn to page 12 of the PDF.

1 A The table or the text?

2 Q The text. And it's going to start at
3 the very first sentence that starts on page 11,
4 but carries over. And you'll see it says, and
5 this is -- let me back up.

6 When you had answered my question
7 previously, you brought me, or you discussed this
8 text on page 11.

9 Do you recall that?

10 A Yes.

11 Q Why does it say that the effects of
12 GLP-1 receptor antagonists on the kidney may
13 include decreases in inflammation, oxidative
14 stress, and fibrosis?

15 MR. ANSTAETT: Objection to form.

16 A It goes back to that paradigm of what
17 are the drivers of diabetic kidney disease and its
18 complexity. And I think using that word, the
19 softer language is almost prudent because that
20 paradigm is not fully locked down and it's
21 probably a little bit of inflammation, a little
22 bit of hypertension, a little bit of oxidative

1 stress, a little bit of advanced (indiscernible)
2 end products. It's some combination of all of
3 that.

4 What the leading scientists are doing
5 is actually trying to subphenotype patients
6 depending on are they -- do they have a more
7 inflammatory phenotype underlying, do they have a
8 more fibrotic, do they have a more, you know,
9 structural-type thing. People working on better
10 compartmentalizing these different
11 pathophysiologic properties. Some of it is
12 redundant and they overlap and they move forward
13 on each other.

14 It's just wise, prudent language
15 because this study certainly does not give us
16 mechanistic insights in itself, so...

17 Q So you're saying it's still not known
18 why semaglutide has these kidney-protective
19 effects, even as of 2024?

20 A With a hundred percent certainty, no.
21 It's not known. But, again, indications are it's
22 some combination, and to what degree on each of

1 these properties inflammation, oxidative stress,
2 fibrosis, is still being worked out.

3 Q But you expected this in 2012, without
4 any public data on semaglutide?

5 MR. ANSTAETT: Objection to form.

6 A Well, a GLP-1 peptide or the analogs
7 receptor antagonists were suggesting, again, there
8 was some data then, again, as time passes, more
9 emerges, that there are some of these -- some of
10 these anti-inflammatory or other -- yeah, some of
11 this anti-fibrotic, anti-inflammatory effects.

12 MR. REICH: I think we can take a break
13 and probably wrap up so we can go off the record.

14 MR. ANSTAETT: Okay.

15 (Recess taken from 2:34 p.m. to
16 2:39 p.m.)

17 BY MR. REICH:

18 Q Dr. Coca, just to be clear, for the
19 record, Exhibit 2604 is the FLOW manuscript that
20 you testified you had reviewed in preparation for
21 today's deposition?

22 A Yes.

1 MR. REICH: Pass the witness.

2 MR. ANSTAETT: Okay. We'll take a
3 break and be back and let you know if we have any
4 questions.

5 (Recess taken from 2:39 p.m. to
6 3:00 p.m.)

7 EXAMINATION BY COUNSEL FOR THE PETITIONERS
8 BY MR. ANSTAETT:

9 Q So, Dr. Coca, I just want to follow up
10 on a couple particular questions that Mr. Reich
11 asked you.

12 Do you recall he asked you some
13 questions about Exhibit 1148? That's the -- the
14 Yu article?

15 A Yes, I recall.

16 Q Okay. And that's an article by Yu,
17 titled "Antihypertensive Effect of GLP-1 in Dahl
18 Salt-Sensitive Rats."

19 Is that right?

20 A Correct.

21 Q What's the date of that publication?
22 Maybe if we scroll down.

1 A 2003.

2 Q And you recall the priority date of the
3 '462 patent here is either 2012 or potentially,
4 according to the patent owners, as early as 2010;
5 is that right?

6 A Correct, that's my understanding.

7 Q And so, how far in advance of the
8 priority date was the Yu article published,
9 approximately?

10 MR. REICH: Objection. Form.

11 A A minimum of, approximately,
12 seven years.

13 Q Okay. And do you recall Mr. Reich read
14 you selected sentences from the Yu article?

15 A Yes, I remember.

16 Q Okay. And if we could turn to page 10
17 of Exhibit 1148, please.

18 And if we scroll down just a bit
19 further. That's good.

20 Do you see there, there's a paragraph
21 that begins with the words "in summary"?

22 A Yes, I see that.

1 Q Okay. And for the record, could you,
2 please, read that full paragraph.

3 A "In summary, the results of the present
4 study indicate that chronic administration of
5 recombinant GLP-1 attenuates the development of
6 hypertension, reduces cardiac and renal end-organ
7 damage, and improves endothelial function in Dahl
8 S rats fed a high-salt diet for two weeks. The
9 antihypertensive effect of recombinant GLP-1 in
10 Dahl S rats appears to be largely due to its
11 diuretic and natriuretic actions to prevent sodium
12 and water retention. Due to the short half-life
13 and the lack of oral bioavailability, the
14 therapeutic potential of R GLP-1, itself, for the
15 treatment of hypertension is probably very
16 limited. However, based on the attractive
17 therapeutic profile of R GLP-1 is to prevent
18 hypertension and renal and cardiac end-organ
19 damage, and orally active and stable GLP-1 analogs
20 might be useful for the treatment of
21 salt-sensitive forms of hypertension and other
22 conditions associated with sodium retention, such

1 as heart failure."

2 Q All right. And that publication was
3 from 2003; is that correct?

4 A Correct.

5 Q And that paragraph, that you just read,
6 referred to the short half-life of R GLP-1.

7 Do you see that?

8 A Yes.

9 Q Okay. By 2010, was there a GLP-1
10 analogue that was stable and did not suffer from
11 the short half-life referred to in Yu?

12 A Yes.

13 MR. REICH: Objection. Scope.

14 Q And what was that?

15 MR. REICH: Objection.

16 Q You can answer.

17 A Liraglutide.

18 Q Okay. If we could look at
19 Exhibit 1147, please.

20 All right. We're looking at

21 Exhibit 1147 now, this is the article

22 "Antihypertensive and Natriuretic Effect of

1 Glucagon-Like Peptide 1 in Dahl S Rats: A Novel
2 Function for a Pleiotrophic Hormone," by
3 Vollenweider.

4 Do you see that?

5 A Yes, I see that.

6 Q Do you recall Mr. Reich asked you some
7 questions about this article?

8 A Yes, I recall.

9 Q What year was Exhibit 1147 published,
10 please?

11 A 2003.

12 Q Is that well before the priority date
13 of the '462 patent?

14 MR. REICH: Objection. Form.

15 A Approximately, seven years.

16 Q Okay. And if we turn to page 2 of the
17 article, and maybe just a little bit further down,
18 that's perfect. Up just once more, up just a bit
19 more. Perfect. Perfect.

20 Okay. Mr. Reich asked you to read a
21 sentence from this article on page 2 that starts
22 "the origin of."

1 Do you see that?

2 A Yes, I see that.

3 Q So this says "the origin of these
4 discrepancies," and he asked you to read that
5 sentence, right?

6 A Correct.

7 Q And he didn't ask you to read the next
8 two sentences.

9 Could you, please, for the record, read
10 the two sentences that follow that sentence.

11 MR. REICH: Objection. Form. Scope.

12 A "Additional experiments directly
13 addressing these issues, particularly in humans,
14 will help to resolve some of these questions.
15 This is important because GLP-1 is under intensive
16 investigation for its therapeutic use in type 2
17 diabetes mellitus."

18 Q Could you read the next sentence,
19 please, as well?

20 A "Indeed, GLP-1 is a very interesting
21 candidate drug for this indication because its
22 insulinotropic actions are maintained in diabetic

1 patients and it has additional beneficial effects,
2 such as decreasing food intake and promoting
3 weight loss, inhibiting gastric emptying and
4 glucagon secretion, and potentially increasing
5 insulin sensitivity and beta cell proliferation."

6 Q All right.

7 And let me ask you, now, to look at
8 another, Exhibit 11 -- Exhibit 1149.

9 MR. ANSTAETT: If you could pull that
10 up, please.

11 Q All right. Exhibit 1149 is an article
12 entitled "Glucagon-Like Peptide 1 Induces
13 Natriuresis in Healthy Subjects and in
14 Insulin-Resistant Obese Men."

15 Do you see that?

16 A Yes, I see that.

17 Q This is the Gutzwiller article that you
18 cited here before, right?

19 A Right.

20 Q Mr. Reich asked you to look at
21 paragraph 79 of your report, your declaration,
22 while he was asking you about this, so I'm going

1 to ask you to do the same.

2 If you'd look at paragraph 79, please.

3 First, let me ask you, when was
4 Gutzwiller published?

5 A 2004.

6 Q Okay. And you cited the Gutzwiller
7 paper from 2004 in paragraph 79 of your
8 declaration, correct?

9 A Correct.

10 Q And you wrote -- you wrote there, by
11 2004 it was "documented that GLP-1 infusion
12 dose-dependently increased sodium excretion and
13 had a natriuretic effect in obese,
14 insulin-resistant patients who suffered from type
15 2 diabetes."

16 Do you see that?

17 A I see that.

18 Q For that, you cited page 6 of the
19 Gutzwiller article; is that right?

20 A Yes.

21 Q Mr. Reich had some objection about
22 where you placed quotation marks in page 79 of

1 your report, with respect to that article.

2 Do you recall that?

3 MR. REICH: Objection. Form.

4 A I recall.

5 Q Okay. Would you, please, and if we --
6 I'm sorry, could we look at page 6 of the
7 Gutzwiller article.

8 If we scroll down, please, below the
9 graphs. Yeah. And that's great. I'm sorry,
10 could you just scroll up just a touch. Perfect.

11 Dr. Coca, I'd like to ask you to read,
12 for the record, a portion that Mr. Reich did not
13 ask you about. Could you read, for the record,
14 the first four sentences of the discussion section
15 of Gutzwiller?

16 A "This study demonstrates that the
17 infusion of synthetic human GLP-1 significantly
18 increased natriuresis in healthy male subjects and
19 in obese, insulin-resistant men. The effects of
20 GLP-1 on the kidney broadened the spectrum of its
21 biological actions of the peptide, in addition to
22 its well-known effects on blood glucose and

1 insulin release. We have previously reported that
2 food and water intake were diminished with
3 continuous GLP-1 infusion in patients suffering
4 from type 2 diabetes mellitus. Here, we have
5 documented that GLP-1 infusion dose-dependently
6 increases urinary sodium excretion in healthy male
7 volunteers."

8 Q And you recall, I think Mr. Reich
9 established with you that the obese,
10 insulin-resistant patients, 25 percent of those
11 were suffering from type 2 diabetes.

12 Is that what this article reports?

13 MR. REICH: Objection.

14 A Yes.

15 Q And in looking at paragraph 79 of your
16 report, do you think you mischaracterized the
17 findings of the Gutzwiller article in any way?

18 MR. REICH: Objection. Form.

19 A I think my characterization was largely
20 in the spirit of the findings, in regards to
21 sodium excretion induced by GLP-1 infusion.

22 Q All right. And, lastly, Dr. Coca, is

1 it uncommon, in your field, for scientific
2 publications to say that their findings should be
3 confirmed in additional studies?

4 MR. REICH: Objection. Form. Scope.

5 A It's a very common refrain that,
6 virtually, all scientists and investigators use in
7 writing their manuscripts.

8 MR. ANSTAETT: Thank you, Dr. Coca. I
9 have no further questions.

10 MR. REICH: Nothing else from us.
11 Thank you, Dr. Coca. I appreciate your time
12 today.

13 THE WITNESS: My pleasure, thank you.

14 MR. ANSTAETT: Thanks, all.

15 (Off the record at 3:11 p.m.)

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1 CERTIFICATE OF REPORTER - NOTARY PUBLIC

2 I, JUDITH E. BELLINGER, RPR, CRR, CSR,
3 the officer before whom the foregoing deposition
4 was taken, do hereby certify that the foregoing
5 transcript is a true and correct record of the
6 testimony given; that said testimony was taken by
7 me and thereafter reduced to typewriting under my
8 direction; that reading and signing was not
9 requested; and that I am neither counsel for,
10 related to, nor employed by any of the parties to
11 this case and have no interest, financial or
12 otherwise, in its outcome.

13 IN WITNESS WHEREOF, I have hereunto set
14 my hand and affixed my notarial seal this 18th day
15 of July, 2024.

16 My Commission Expires: November 3, 2024

17
18
19 *Judith E. Bellinger*
20 _____

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a1	absorption	150:11, 153:22,	administer
102:5	77:16	156:21	32:13, 88:18,
a2	abstract	activation	89:9
102:5	79:7, 91:20,	26:21	administered
a3	137:21, 138:17	active	45:5, 86:4,
102:5	abundant	23:17, 48:8,	98:18
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